

**AMENDMENTS TO THE DRAWINGS**

The figures are amended herein to be in compliance with 37 C.F.R. § 1.84(u). Particularly, the figures are now identified by a number followed by an upper case letter. Also, Figure 1B is amended to properly identify parts (a) and (b). The specification also is amended to reflect the changes in the drawings. The amendments to the drawings and specification do not represent new matter.

Attachment as Appendix A: Replacement sheet

Annotated sheet showing changes

### REMARKS

Claims 37, 42, 44, and 49 are amended herein. Claims 37 and 44 are amended to cancel non-elected subject matter within those claims. Claims 38-41 and 45-48 are canceled herein without prejudice. Applicants reserve the right to pursue the subject matter of the canceled claims in future prosecution. Claims 42 and 49 are amended herein to depend from pending claims 37 and 44, respectfully. Claims 37, 42, 44, and 49 are currently pending.

#### I. The Outstanding Rejections

The drawings stand objected to for not being compliant with 37 C.F.R. § 1.84(u).

A Double Patenting Warning is advised with respect to claims 38, 39, 42, 45, 46, and 49.

Claims 37-42 and 44-49 stand rejected under 35 U.S.C. § 103(a) as assertedly unpatentable over Kosik et al. (Proc. Natl. Acad. Sci., USA, 1986, Vol. 83, pp. 4044-8) ("Kosik") in view of Harlow and Lane, 1988 (Antibodies, Laboratory Manual, Cold Spring Laboratory, pp. 77, 96-97) ("Harlow and Lane").

Claims 37-42 and 44-49 stand rejected under 35 U.S.C. § 103(a) as assertedly unpatentable over Vooheis, U.S. Patent No. 5,492,812 ("Vooheis") in view of Harlow and Lane, 1988 (Antibodies, Laboratory Manual, Cold Spring Laboratory, pp. 77, 96-97).

#### II. Patentability Arguments

##### Double Patenting

Claims 38, 39, 45, and 46 are canceled herein without prejudice. The cancellation of these claims renders the Warning moot.

##### Obviousness

The rejection maintains that the term "consisting essentially of" should be construed as "comprising." Applicants respectfully disagree. As MPEP § 2111.03 states, "[t]he transitional phrase 'consisting essentially of' limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention. (emphasis in original)

The inventors have determined that tau protein that is phosphorylated at Serine 262 specifically occurs in Alzheimer paired helical filaments. A "basic" and "novel" characteristic of the present invention is that the compositions and methods are useful for the production of antibodies that differentiate between tau protein that is phosphorylated at Serine 262 versus tau protein that is not. As was understood by those of skill in the art at the time of filing, the length and composition of the peptide materially affects the ability of the peptide to consistently elicit antibodies that bind the original protein. (Harlow and Lane, page 76; Appendix B) Those of skill in the art at the time of filing, however, also understood that it may be helpful to add one or a few additional amino acids to the peptide and this addition may not materially affect the peptide. (Harlow and Lane, page 77) Thus, it would be understood in the art that additions may be made to the peptide recited to the claims without materially affecting the ability of the peptide to produce antibodies to an epitope containing Serine 262 but certain other additions may materially affect this ability.

The recitation of a peptide "consisting essentially of" the specified tau amino acid sequence in the claims is entirely appropriate because it excludes materials that materially affect the peptides ability to elicit an immune response such to produce antibodies specific to an epitope comprising Serine 262. On the other hand, it is inappropriate to interpret the claim phrase "consisting essentially of" as "comprising" because certain materials when added to the peptide would affect the novel and basic characteristics of the claimed invention, i.e., the ability of the recited peptide sequence to produce antibodies that recognize an epitope containing Serine 262. Thus, Applicants respectfully request that the Examiner reconsider the interpretation of the claim phrase "consisting essentially of" as "comprising."

Nonetheless, even if the phrase is interpreted as "comprising," the cited art does not render the present claims unpatentable.

Claims 37-42 and 44-49 stand rejected as assertedly unpatentable over Kosik in view of Harlow and Lane. Kosik describes the use of purified paired helical filaments containing tau to produce antibodies in rabbits. The rejection asserts that because it was well know in the art at the time of filing to conjugate peptides to carrier molecules for better immunogenic results (Harlow and Lane), it would have been obvious to conjugate the purified helical filaments to a carrier molecule. The rejection further asserts that one of skill in the art would

have been motivated to do so to enhance the immune response to the paired helical fragments. Applicants respectfully disagree.

The rejection cites Harlow and Lane pages 77 as describing the coupling of peptides to a carrier protein. When Harlow and Lane is taken as a whole, however, it is apparent that one of skill in the art would not view the paired helical filaments of Kosik as "peptides" to be conjugated to a carrier molecule. Pages 75-76 of Harlow and Lane are provided as Appendix B. Discuss therein are parameters for choosing which portion of a protein and what size the portion should be that will consistently elicit antibodies that bind the original protein. Importantly, the maximum size suggested is only 40 amino acids. In light of that suggested limitation, one of skill in the art would not view the paired helical filaments which Kosik describes as a heterogeneous mixture of polypeptides containing tau, which phosphoproteins range from 50-70 kDa (page 4044, right column), as a "peptide" suitable for conjugation to a carrier protein. Thus, even if "consisting essentially of" is interpreted as "comprising," the rejection fails to put forth a *prima facie* case of obviousness because the cited art does not indicate that one of skill in the art would be motivated to conjugate the paired helical filaments of Kosik to a carrier molecule.

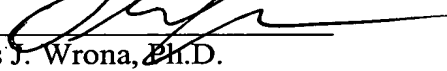
Claims 37-42 and 44-49 stand rejected as assertedly unpatentable over Vooheis in view of Harlow and Lane. The peptide sequence recited in the present claims corresponds to amino acids 201-209 of SEQ ID NO:2 in Vooheis, which is 351 amino acids in length. As discussed above, one of ordinary skill in the art at the time of filing not view the 351 amino acid polypeptide as a "peptide" to be conjugated to a carrier protein. Furthermore, Vooheis does not provide direction or motivation to those of skill in the art to chose the peptide recited in the claims from the myriad of possible peptides encoded in SEQ ID NO:2 of Vooheis. Thus, the rejection fails to establish a *prima facie* case of obviousness and, thus, should be withdrawn.

Conclusion

In view of the above arguments and amendments, applicant believes the pending application is in condition for allowance. Should the Examiner wish to discuss any issues of form or substance in order to expedite allowance of the pending application, the Examiner is invited to contact the undersigned attorney at the number indicated below.

Dated: December 10, 2004

Respectfully submitted,

By   
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Attorney for Applicant

Attachments

Application No.: 09/640,737

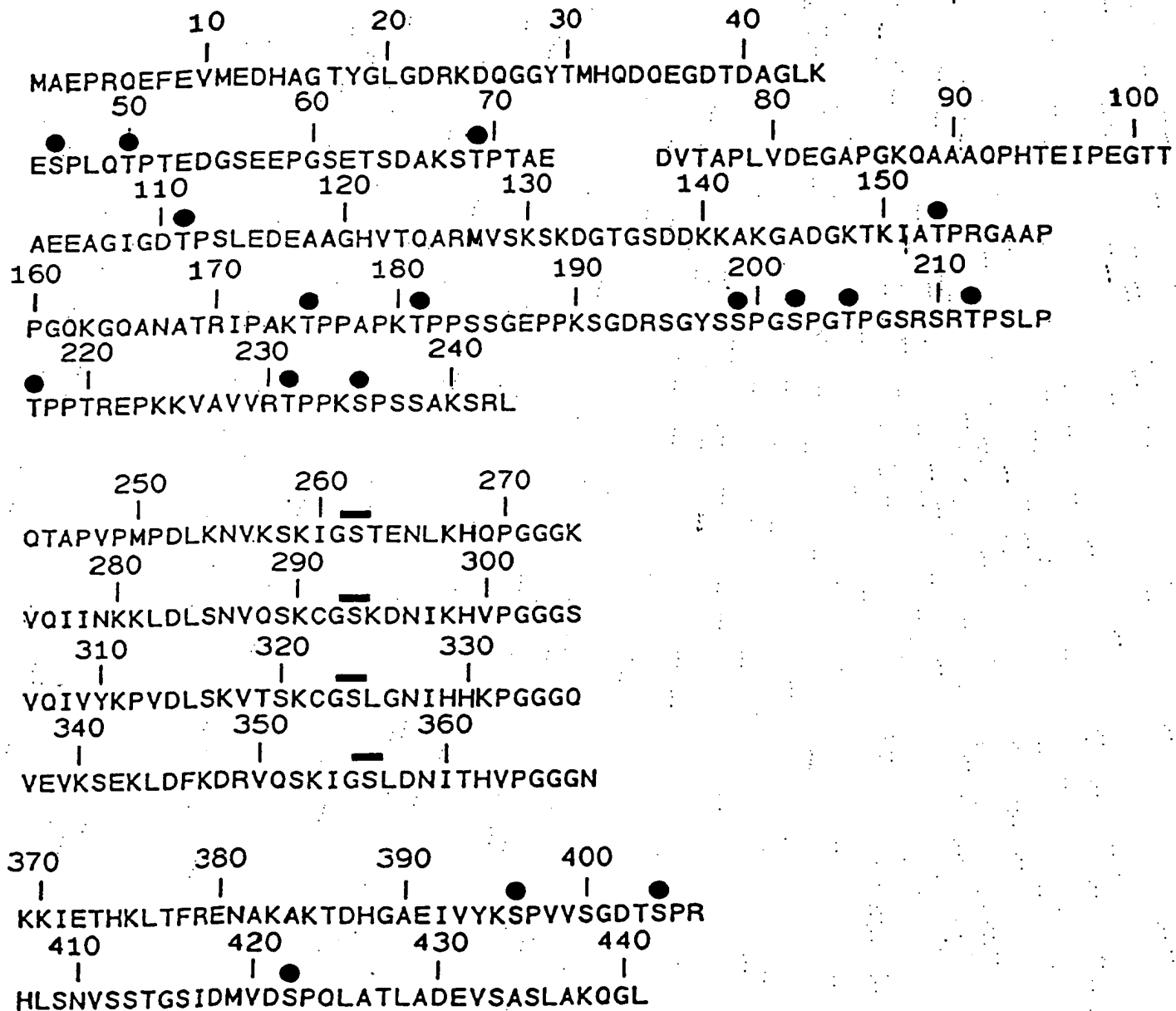
Docket No.: 28384/36668



## **APPENDIX A**

NOVEL TOOLS FOR THE DIAGNOSIS AND  
TREATMENT OF ALZHEIMER'S DISEASE  
MANDELKOW ET AL. U.S.S.N. 09/640,737  
ATTORNEY DOCKET NO. 28384/36668  
ANNOTATED SHEET

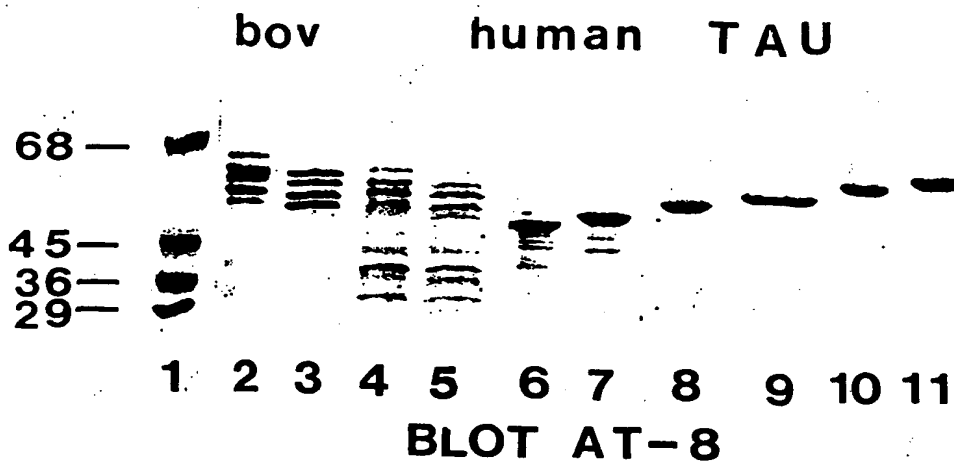
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[Fig. 1a]  
FIGURE 1A

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FIGURE 1A



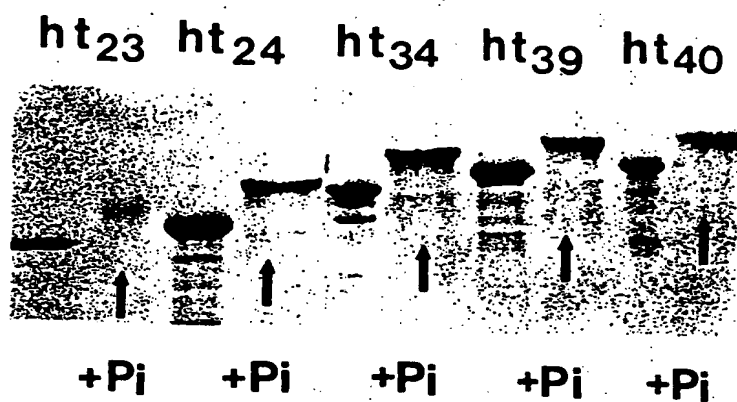
[Fig. 1b]

FIGURE 1B



NOVEL TOOLS FOR THE DIAGNOSIS AND  
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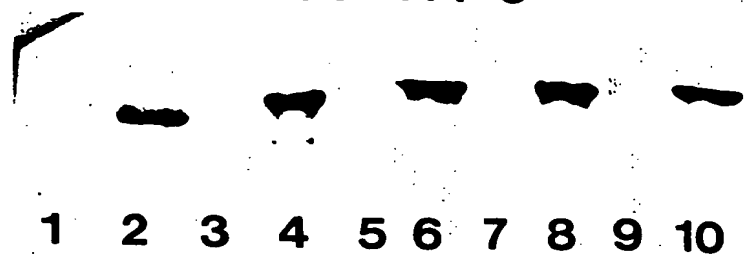
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[Fig. 2a]

FIGURE 2A

BLOT AT-8



[Fig. 2b]

FIGURE 2B

NOVEL TOOLS FOR THE DIAGNOSIS AND  
TREATMENT OF ALZHEIMER'S DISEASE  
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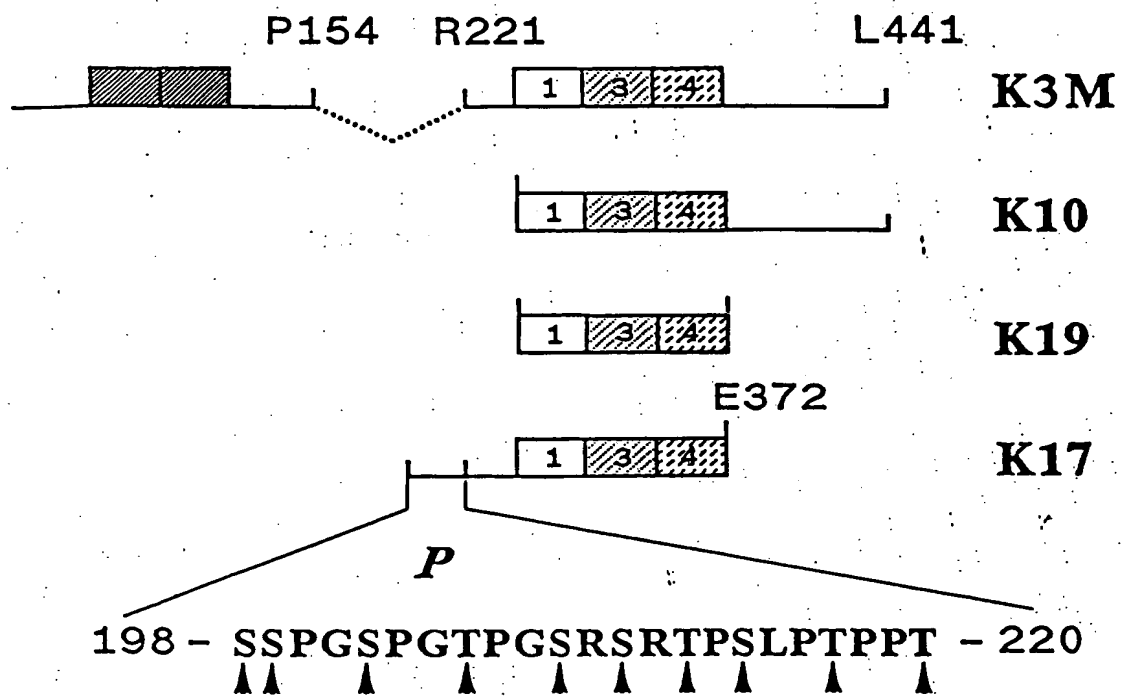
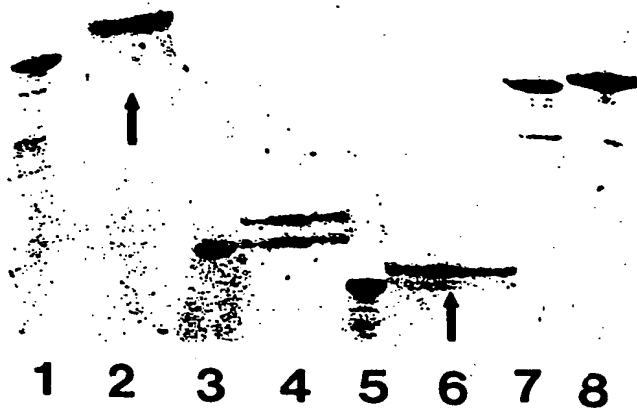


Fig.3

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PAGE

ht<sub>40</sub> K<sub>10</sub> K<sub>17</sub> K<sub>3M</sub>

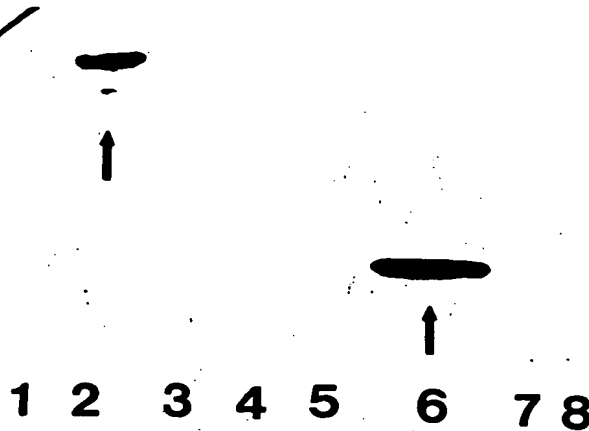


[Fig. 4a]

FIGURE 4A

BLOT-AT8

ht<sub>40</sub> K<sub>17</sub>

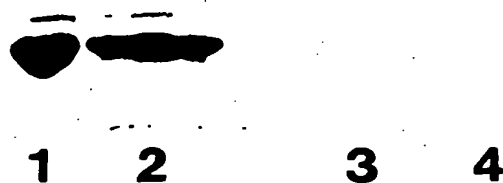


[Fig. 4b]

FIGURE 4B

K<sub>19</sub>

AT-8



[Fig. 4c]

FIGURE 4C

NOVEL TOOLS FOR THE DIAGNOSIS AND  
TREATMENT OF ALZHEIMER'S DISEASE

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htau 23

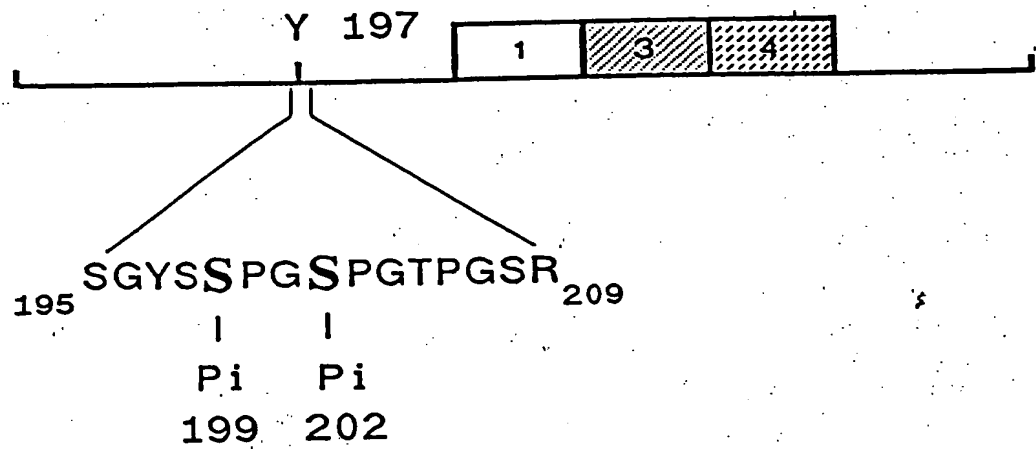


Fig.5

NOVEL TOOLS FOR THE DIAGNOSIS AND  
TREATMENT OF ALZHEIMER'S DISEASE  
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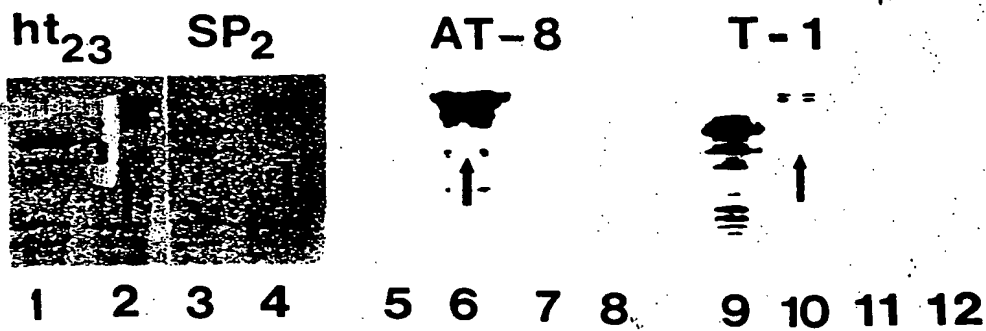


Fig. 6

NOVEL TOOLS FOR THE DIAGNOSIS AND  
TREATMENT OF ALZHEIMER'S DISEASE

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FIGURE 7A

[Fig. 7a]

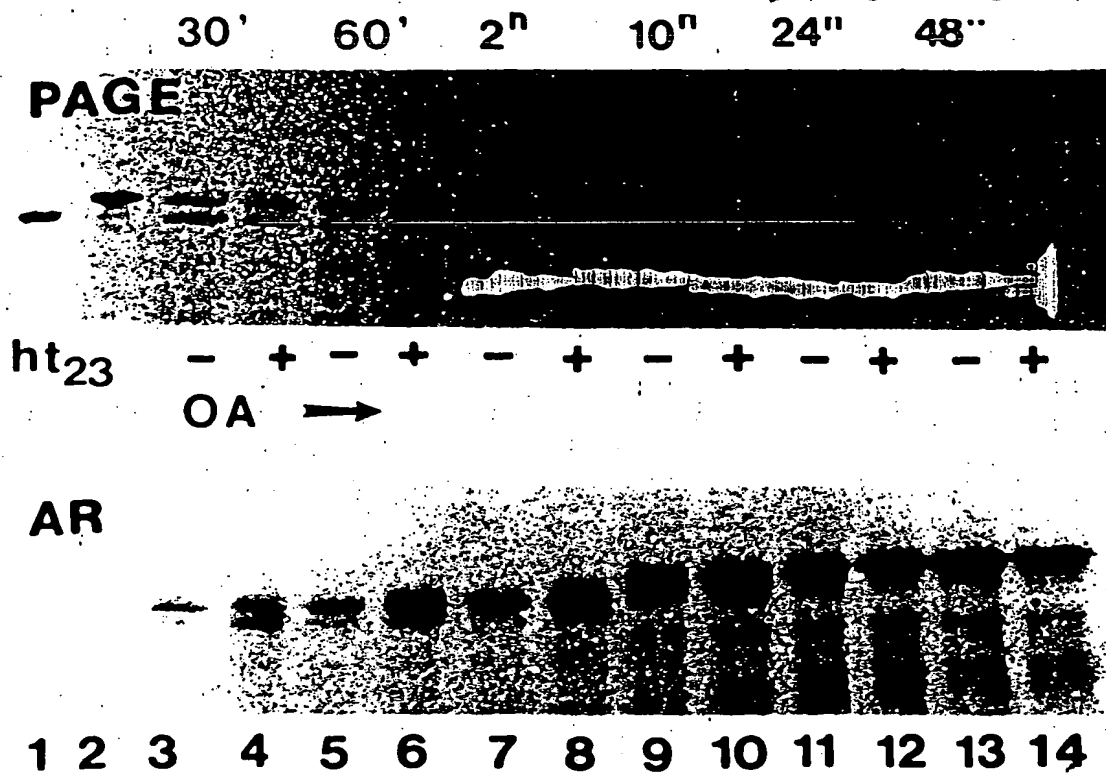
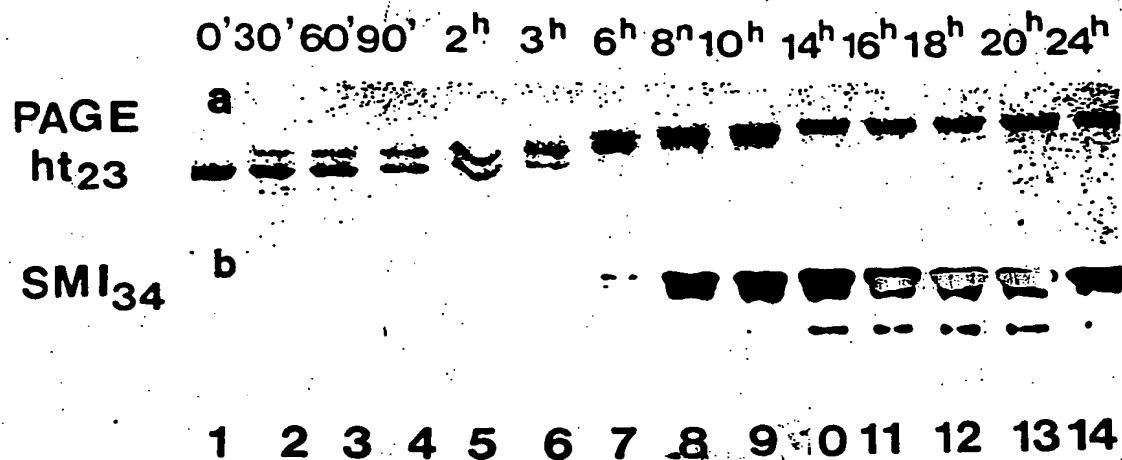


FIGURE 8A  
[Fig. 8a]

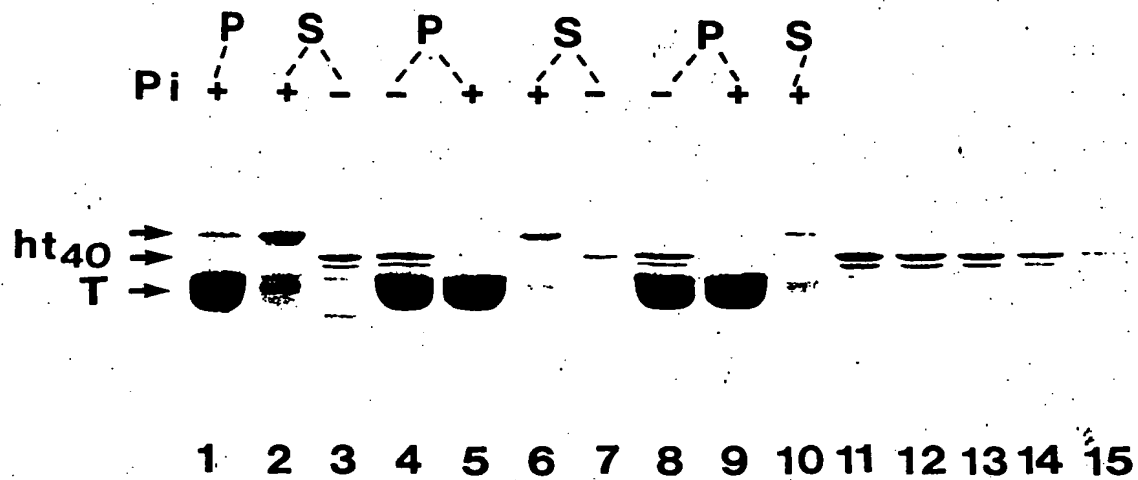
[Fig. 7b]  
FIGURE 7B



[Fig. 8b]  
FIGURE 8B

NOVEL TOOLS FOR THE DIAGNOSIS AND  
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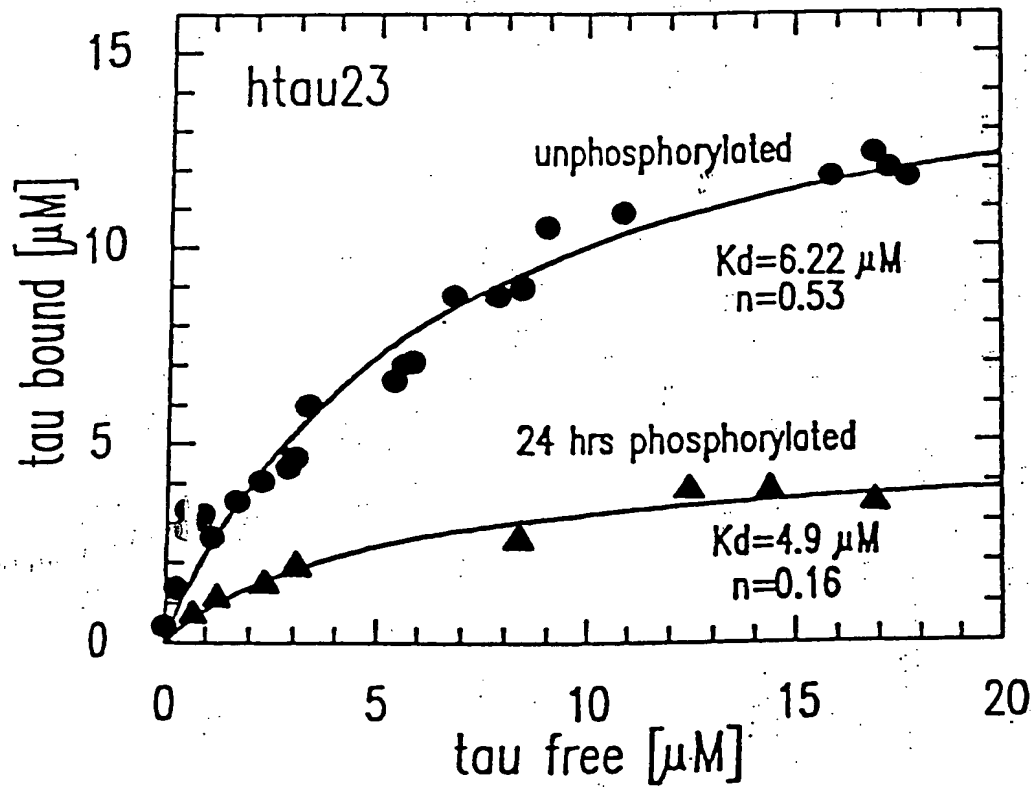
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[Fig. 9a]  
FIGURE 9A

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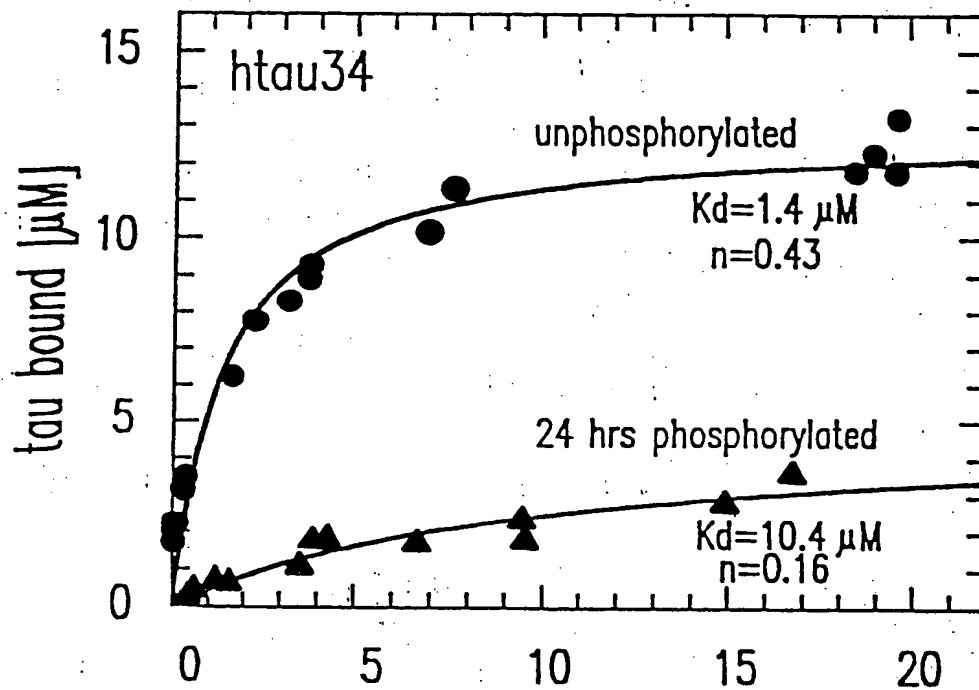
[Fig. 9b]  
FIGURE 9B

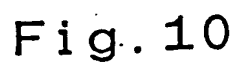




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FIGURE 9C  
[Fig. 9c]





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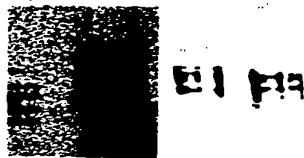
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FIGURE 12A

[Fig. 12a]

ht PHF-t

- + + -



1 2 3 4

FIGURE 12C

[Fig 12c]

SMI<sub>31</sub>

- + + -



1 2 3 4

SMI<sub>33</sub>



1 2 3 4

SMI<sub>34</sub>



1 2 3 4

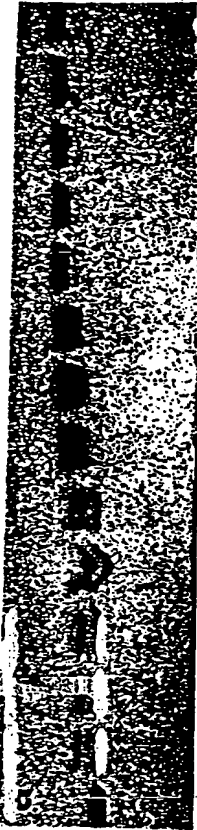
[Fig. 12b]

FIGURE 12B

[Fig. 12d]

FIGURE 12D

0°30'60" 2" 3" 6" 8" 10" 14" 16" 18" 20" 24"



b



PAGE  
ht23

SML31

SML34

SML33

[Fig. 13a]  
FIGURE 13A

[Fig. 13b]  
FIGURE 13B

[Fig. 13c]  
FIGURE 13C

[Fig. 13d]  
FIGURE 13D

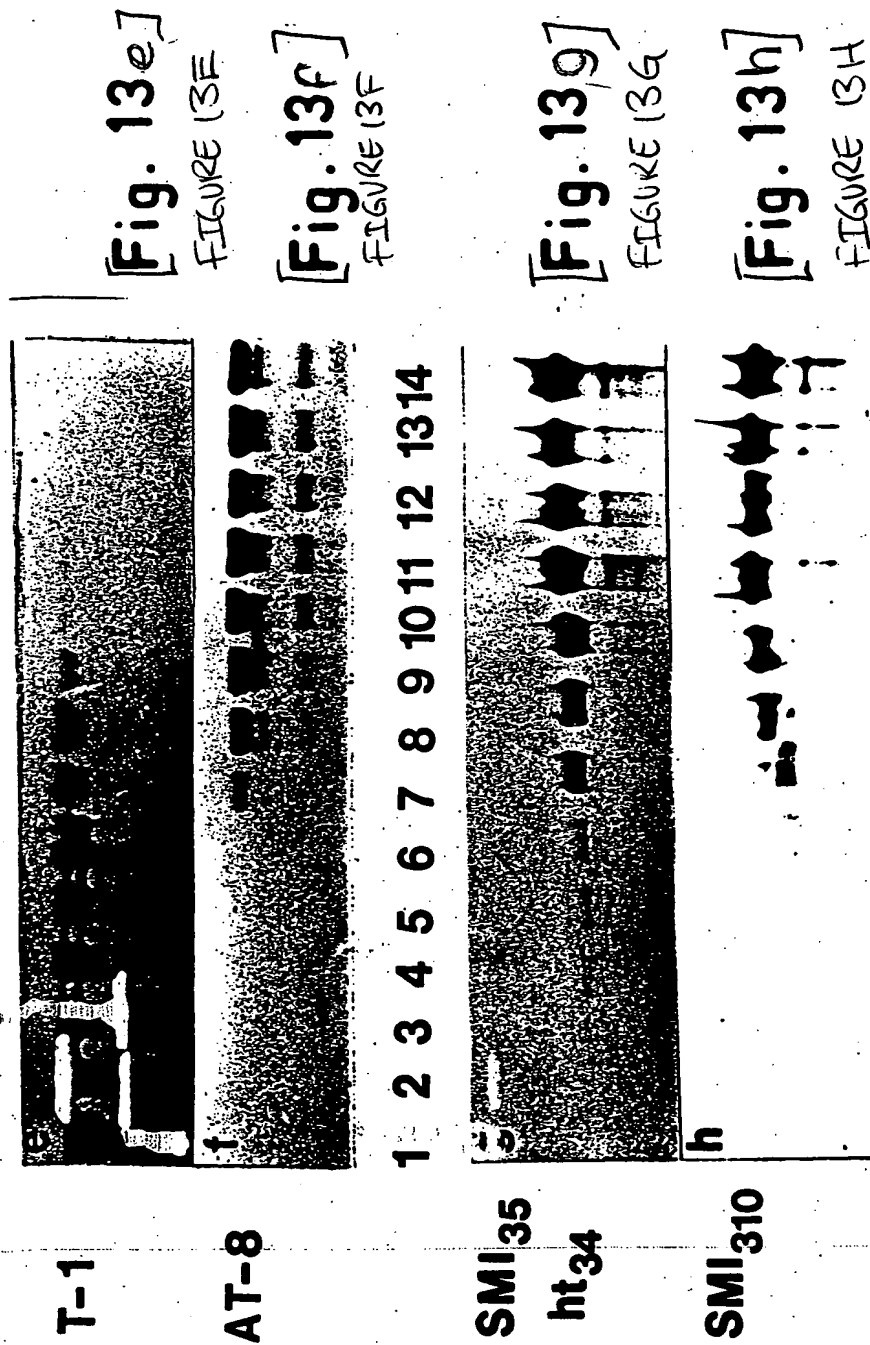
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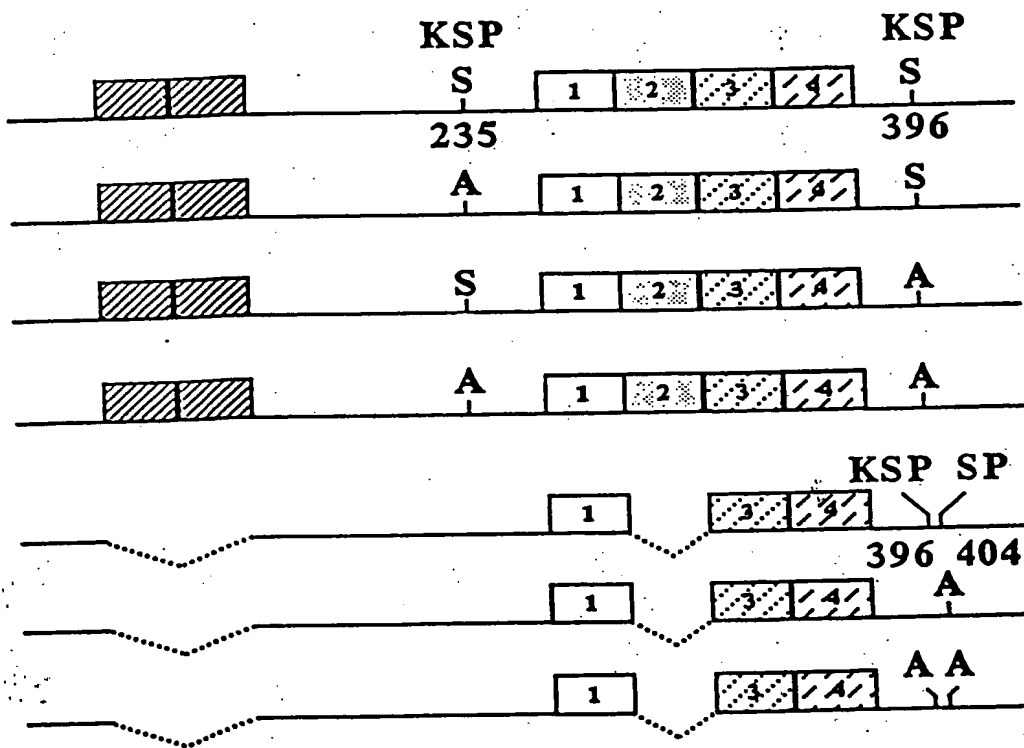
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htau40 FIGURE 15A

A235 FIGURE 15B

A396 FIGURE 15C

A235/396 FIGURE 15D

htau23 FIGURE 15E

A404 FIGURE 15F

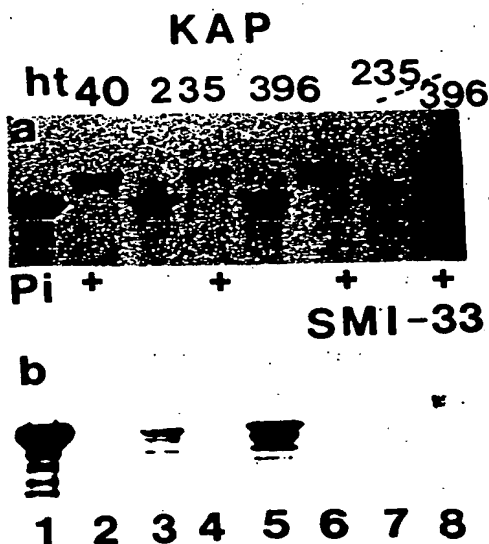
A396/404 FIGURE 15G

[Fig. 15]

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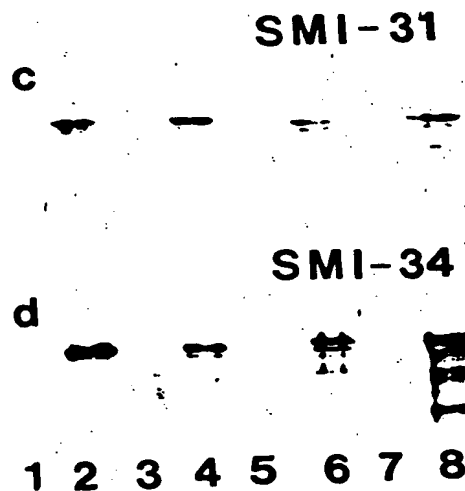
FIGURE 14A  
[Fig. 14a]



[Fig. 14b]

FIGURE 14B

FIGURE 14C  
[Fig. 14c]



[Fig. 14d]

FIGURE 14D

FIGURE 16A  
[Fig. 16a]

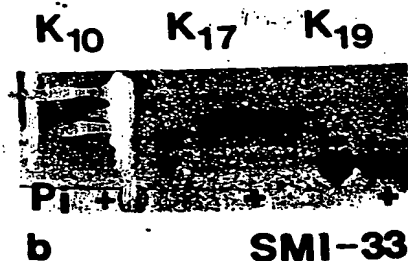


FIGURE 16B

[Fig. 16b]

FIGURE 16C  
[Fig. 16c]

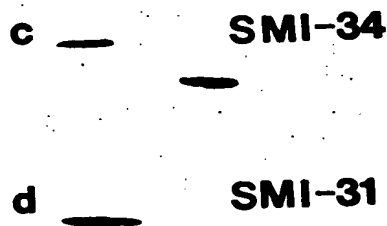
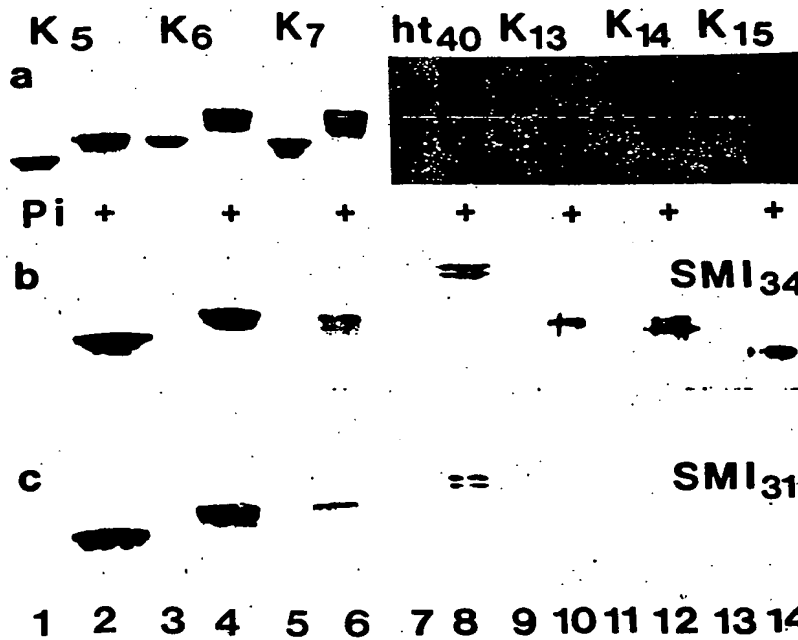


FIGURE 16D

[Fig. 16d]

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[Fig. 17a]

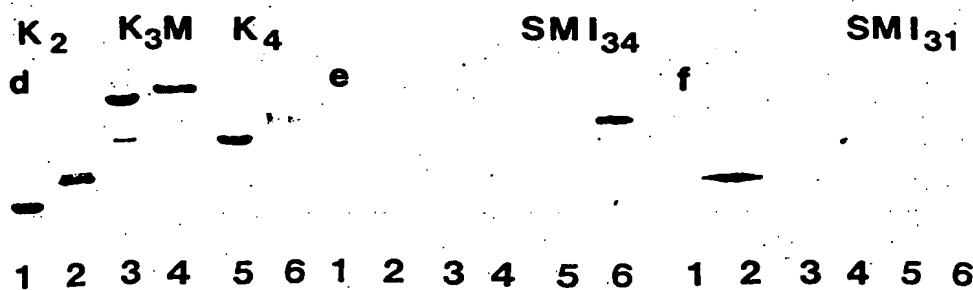
FIGURE 17A

[Fig. 17b]

FIGURE 17B

[Fig. 17c]

FIGURE 17C



[Fig. 17d]

FIGURE 17D

[Fig. 17e]

FIGURE 17E

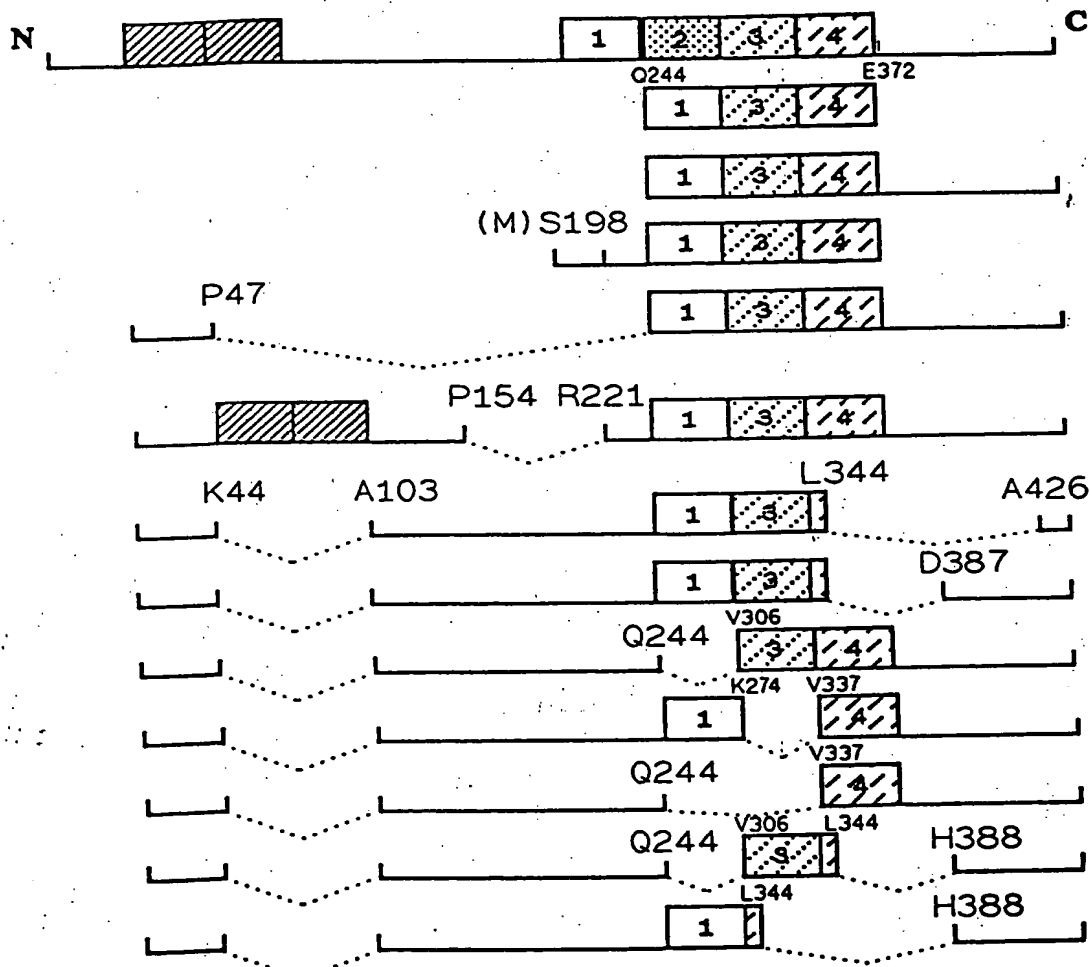
[Fig. 17f]

FIGURE 17F



NOVEL TOOLS FOR THE DIAGNOSIS AND  
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[Fig. 18]

htau40 FIGURE 18A

K19 FIGURE 18B

K10 FIGURE 18C

K17 FIGURE 18D

K2 FIGURE 18E

K3M FIGURE 18F

K4 FIGURE 18G

K5 FIGURE 18H

K6 FIGURE 18I

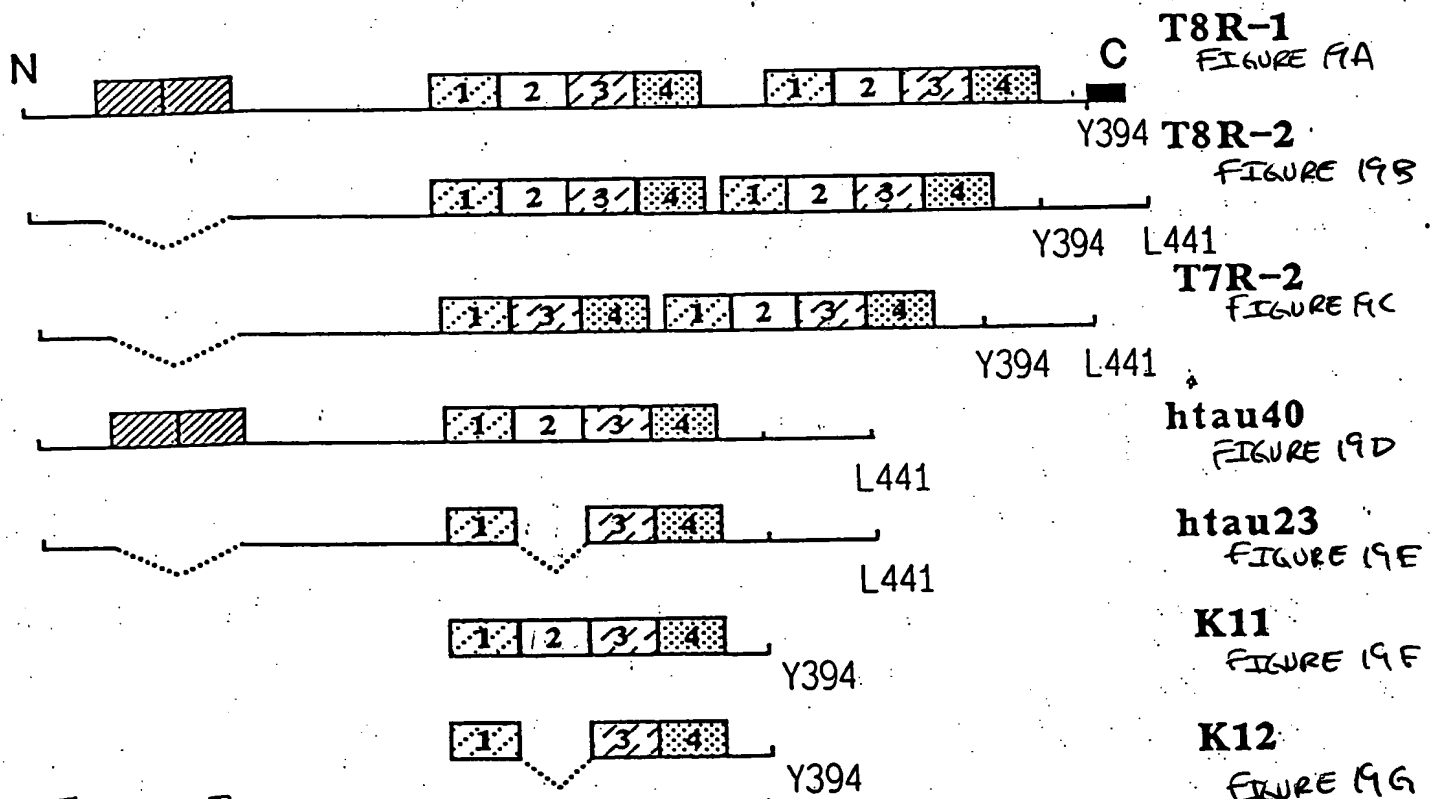
K7 FIGURE 18J

K13 FIGURE 18K

K14 FIGURE 18L

K15 FIGURE 18M

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[Fig. 19]

# ANNOTATED SHEET

**A**

TBR-1 HTau23 K12

97 — —  
66 — —  
45 — —  
18 — —

**B**

+DTT -DTT PDM MBS

66 — —  
45 — —  
29 — —  
14 — —

**C** Fractions

16 17 18 19 20 21

—Te —  
—Tr —  
—D —  
—M —

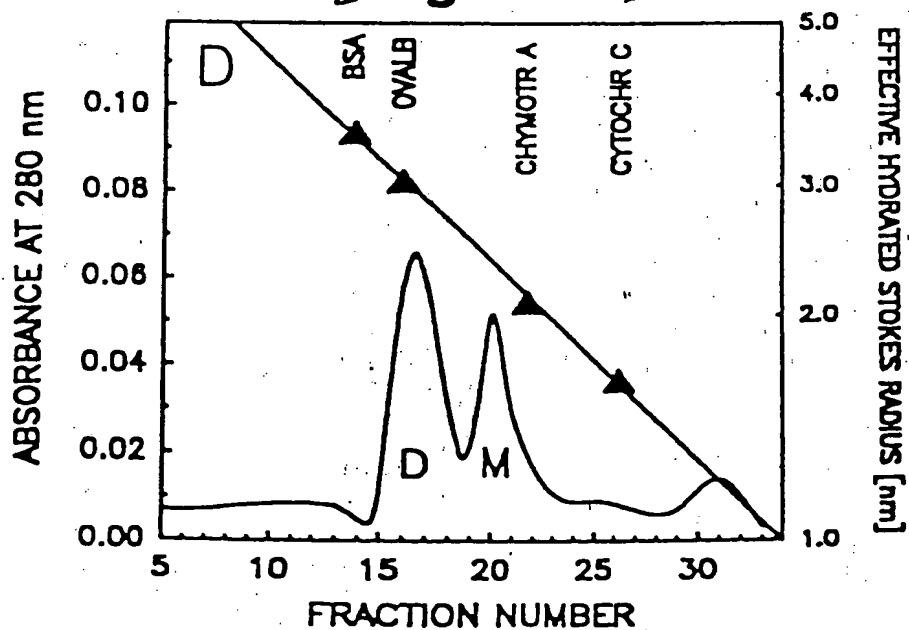
**FIGURE 20A** **FIGURE 20B** **FIGURE 20C**

**[Fig. 20a]** **[Fig. 20b]** **[Fig. 20c]**

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FIGURE 20D

[Fig. 20d]



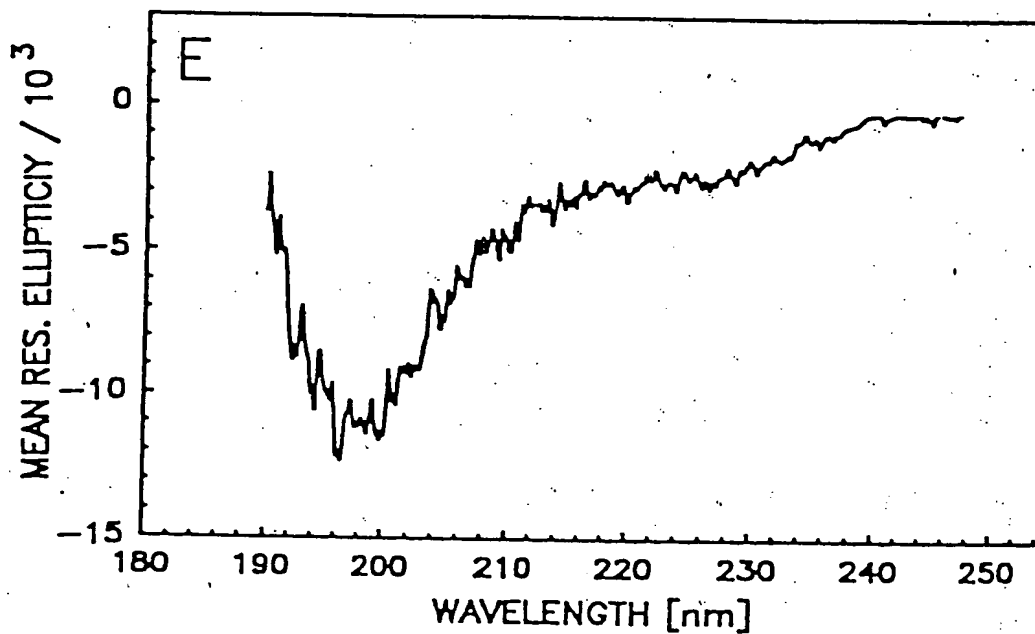
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TREATMENT OF ALZHEIMER'S DISEASE

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[Fig. 20e]

FIGURE 20E

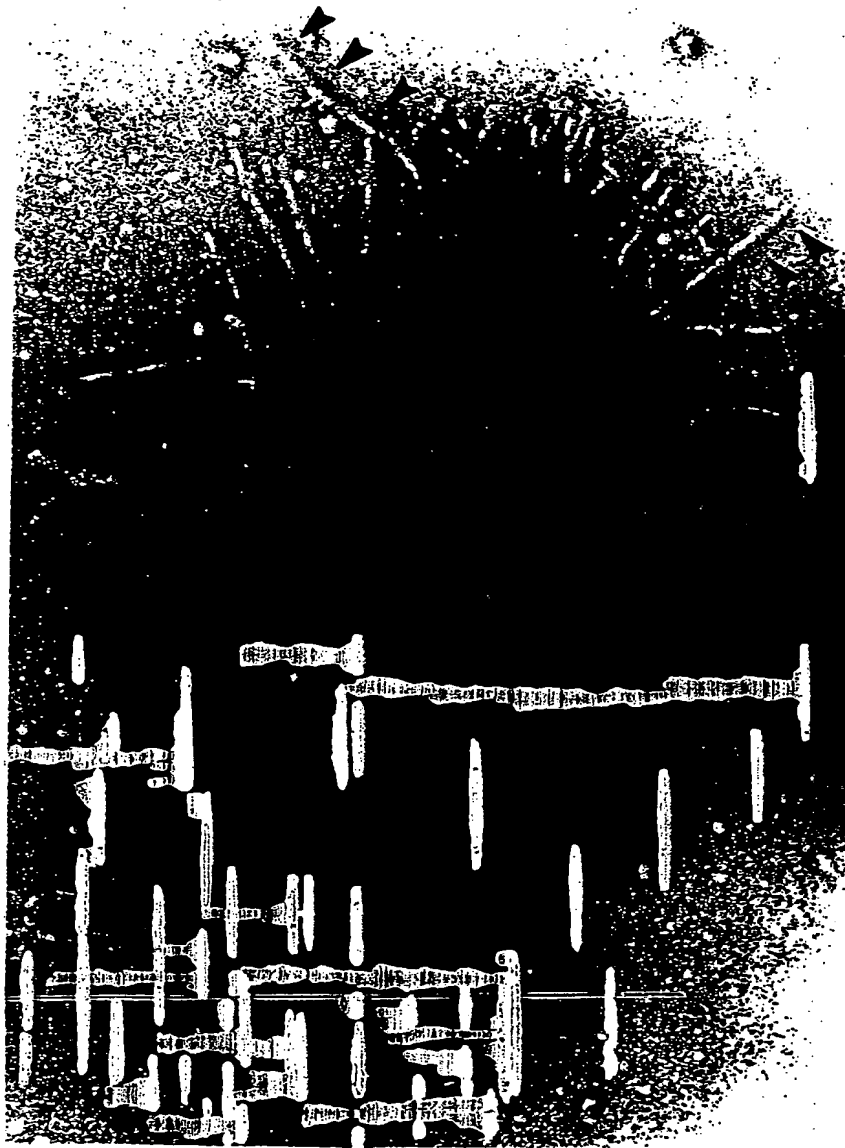
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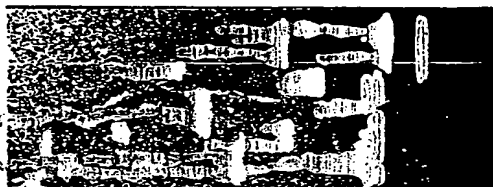
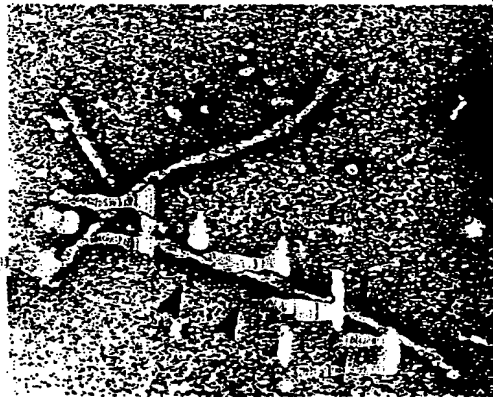
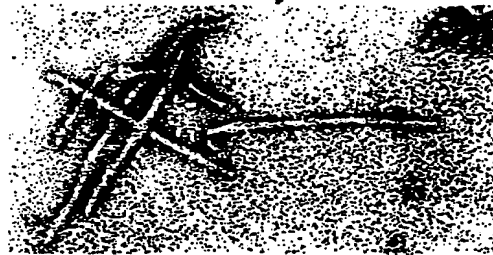
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[Fig. 21a]

FIGURE 21A

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[Fig. 21d] [Fig. 21e]

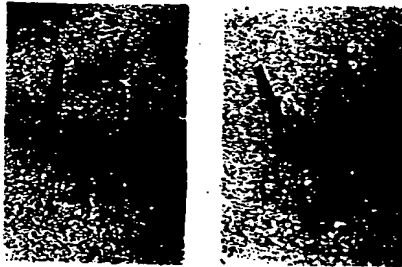
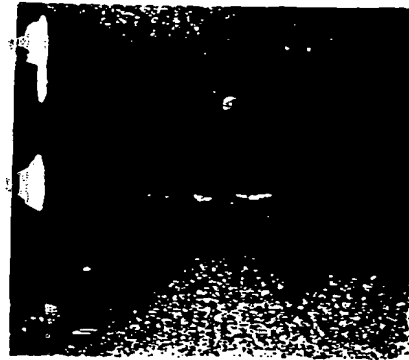
FIGURE 21D: FIGURE 21E

[Fig. 21b] [Fig. 21c]

FIGURE 21B FIGURE 21C

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FIGURE 21f  
[Fig. 21f]

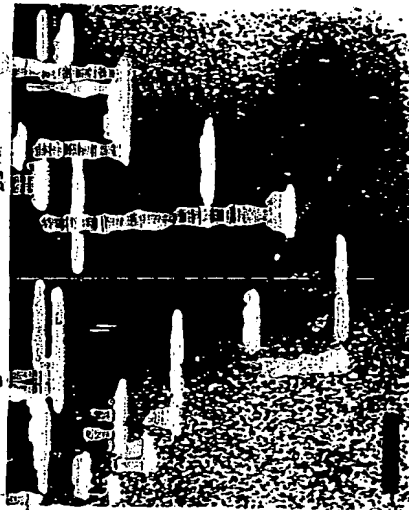


[Fig. 21g] [Fig. 21h] [Fig. 21i]

FIGURE 21h FIGURE 21i

[Fig. 21g]

FIGURE 21g





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FIGURE 22c

[Fig. 22c]



FIGURE 22a

[Fig. 22a]



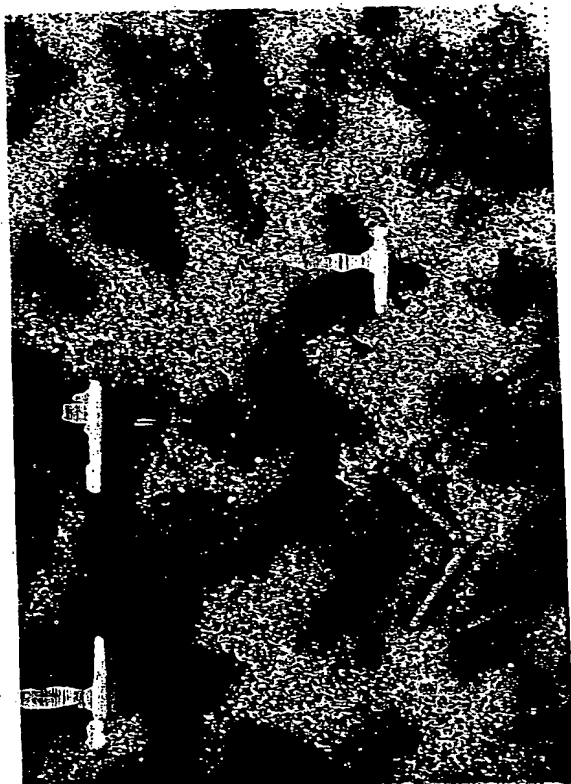
PHFs from K12 PDM dimers

[Fig. 22b]

FIGURE 22b

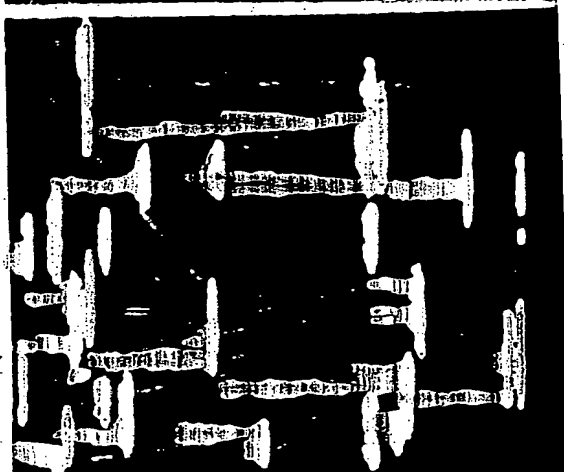
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[Fig. 23b]

FIGURE 23B



[Fig. 23a]

FIGURE 23A

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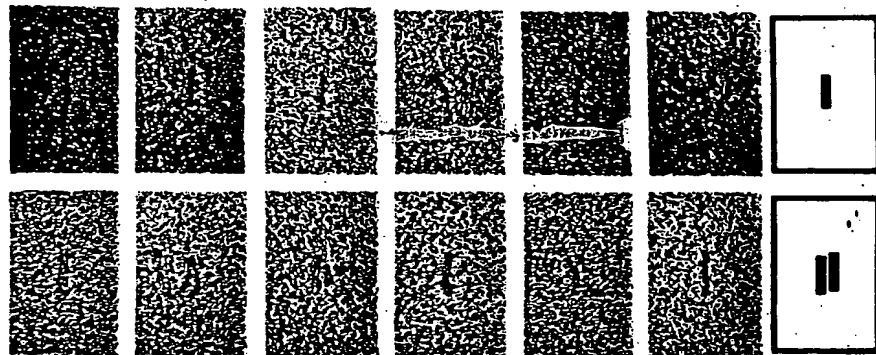


FIGURE 24A  
[Fig. 24a]

FIGURE 24B  
[Fig. 24b]

HTau23

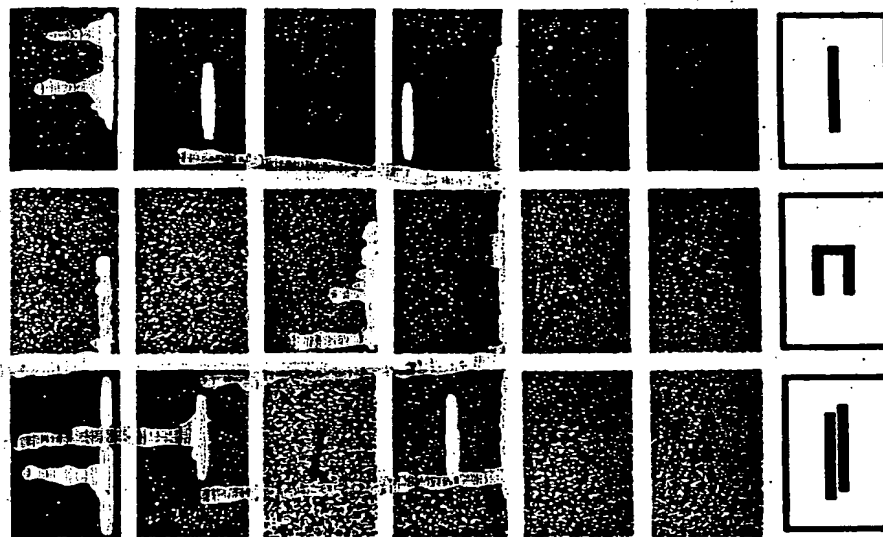


FIGURE 24C  
[Fig. 24c]

FIGURE 24D  
[Fig. 24d]

FIGURE 24E  
[Fig. 24e]

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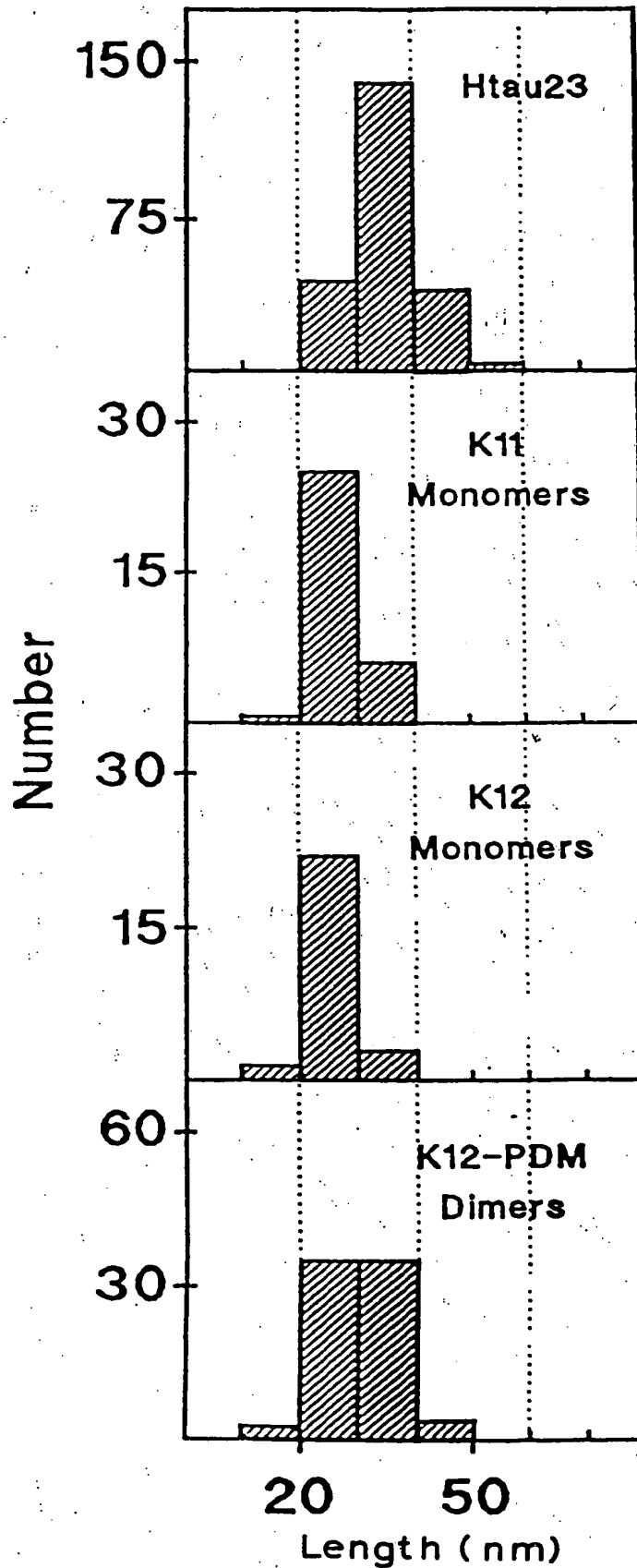


FIGURE 25A  
[Fig. 25a]

FIGURE 25C  
[Fig. 25c]

FIGURE 25E  
[Fig. 25e]

FIGURE 25G  
[Fig. 25g]

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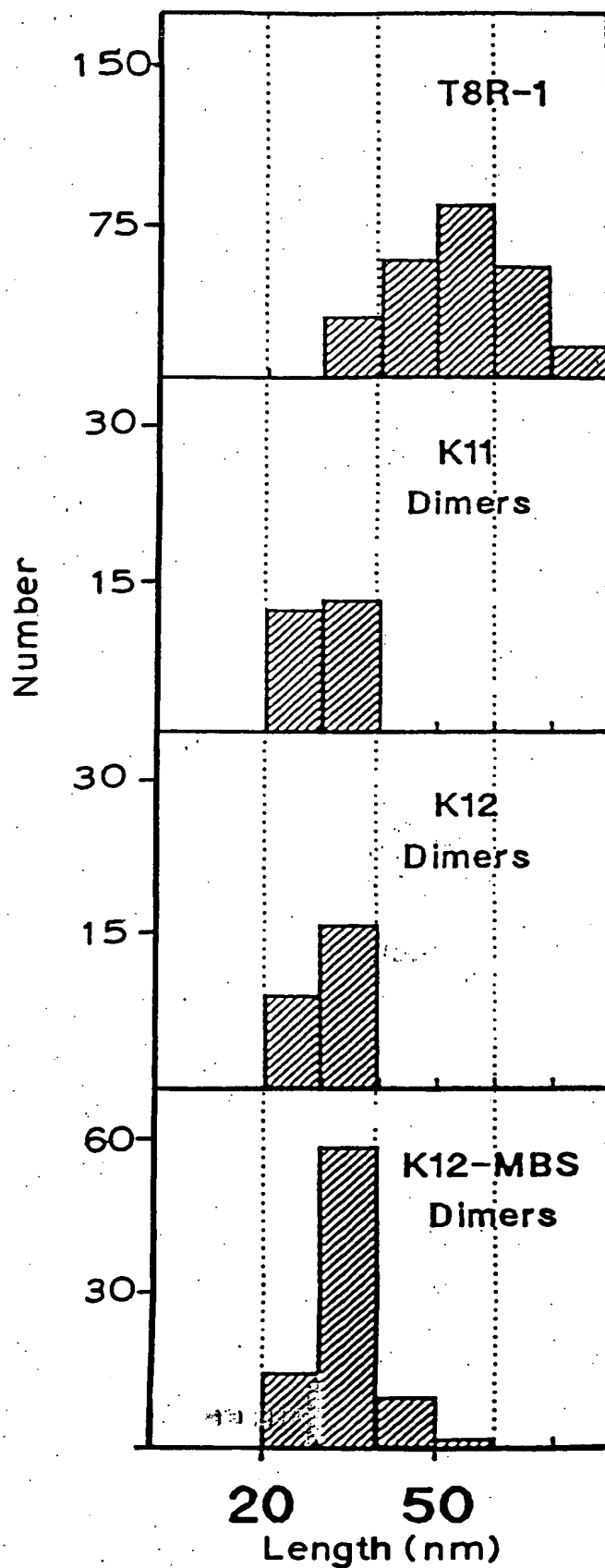


FIGURE 25B  
[Fig. 25b]

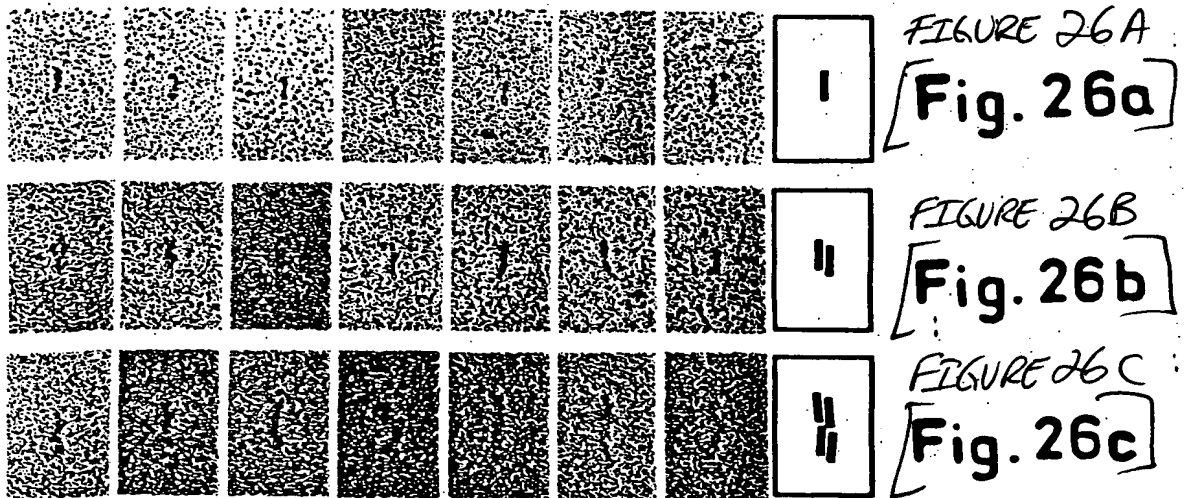
FIGURE 25D  
[Fig. 25d]

FIGURE 25F  
[Fig. 25f]

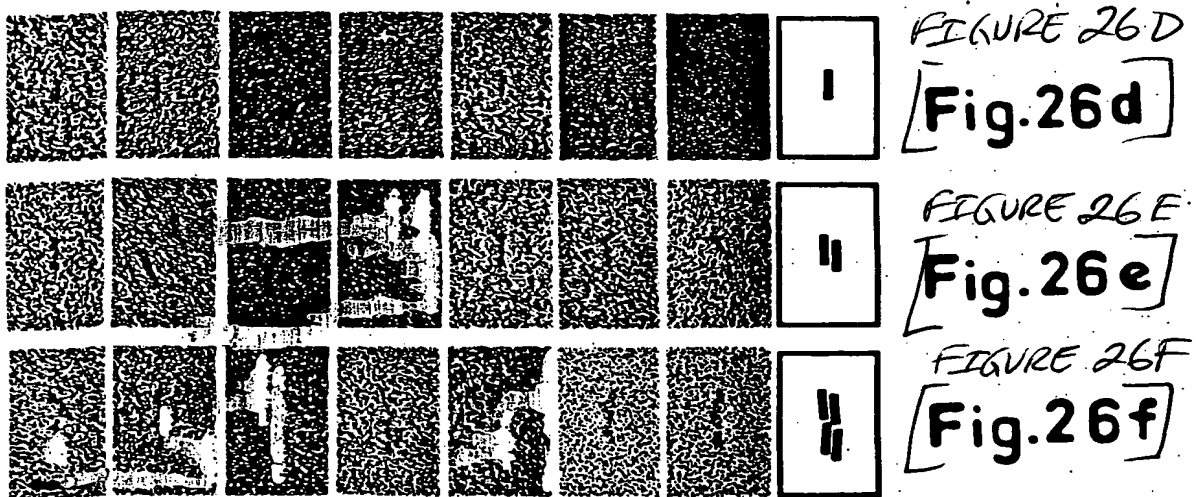
FIGURE 25H  
[Fig. 25h]

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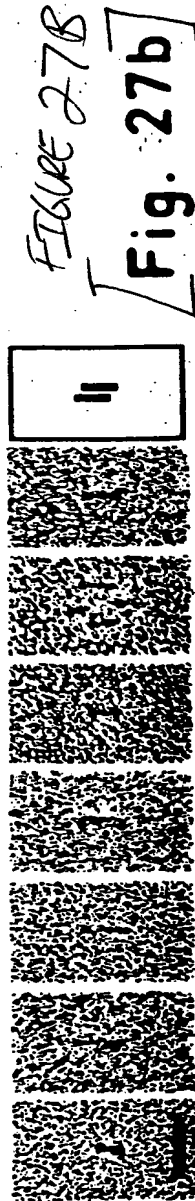
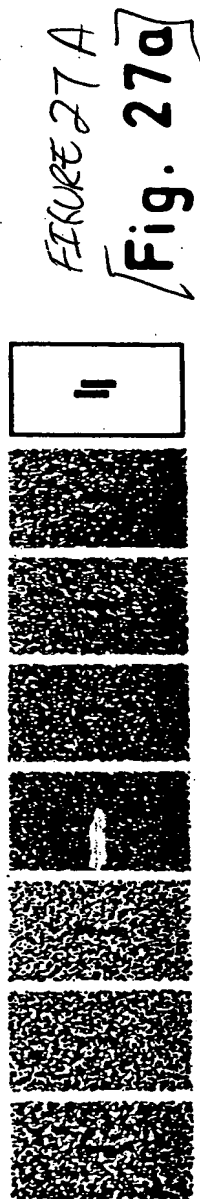


K11



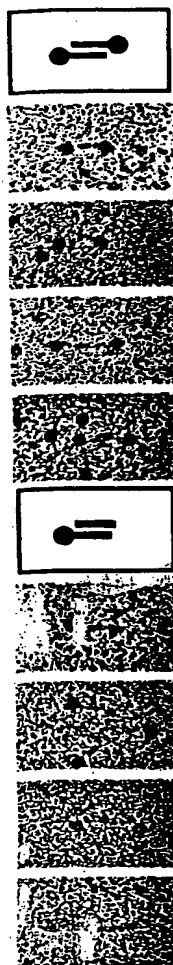
K12

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FIGURE 28A  
[Fig. 28a]



Htau23 + AB2-4

FIGURE 28B  
[Fig. 28b]



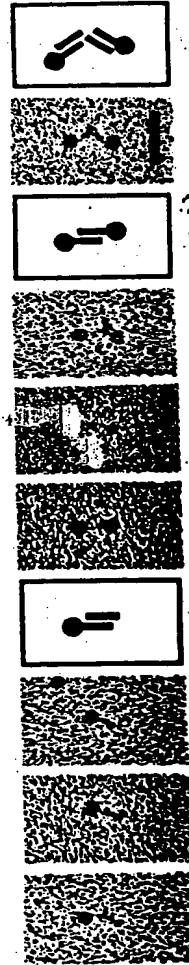
K12 + AB2-4

FIGURE 28C  
[Fig. 28c]



K12 PDM dimer + AB2-4

FIGURE 28D  
[Fig. 28d]



K12 MBS dimer + AB2-4



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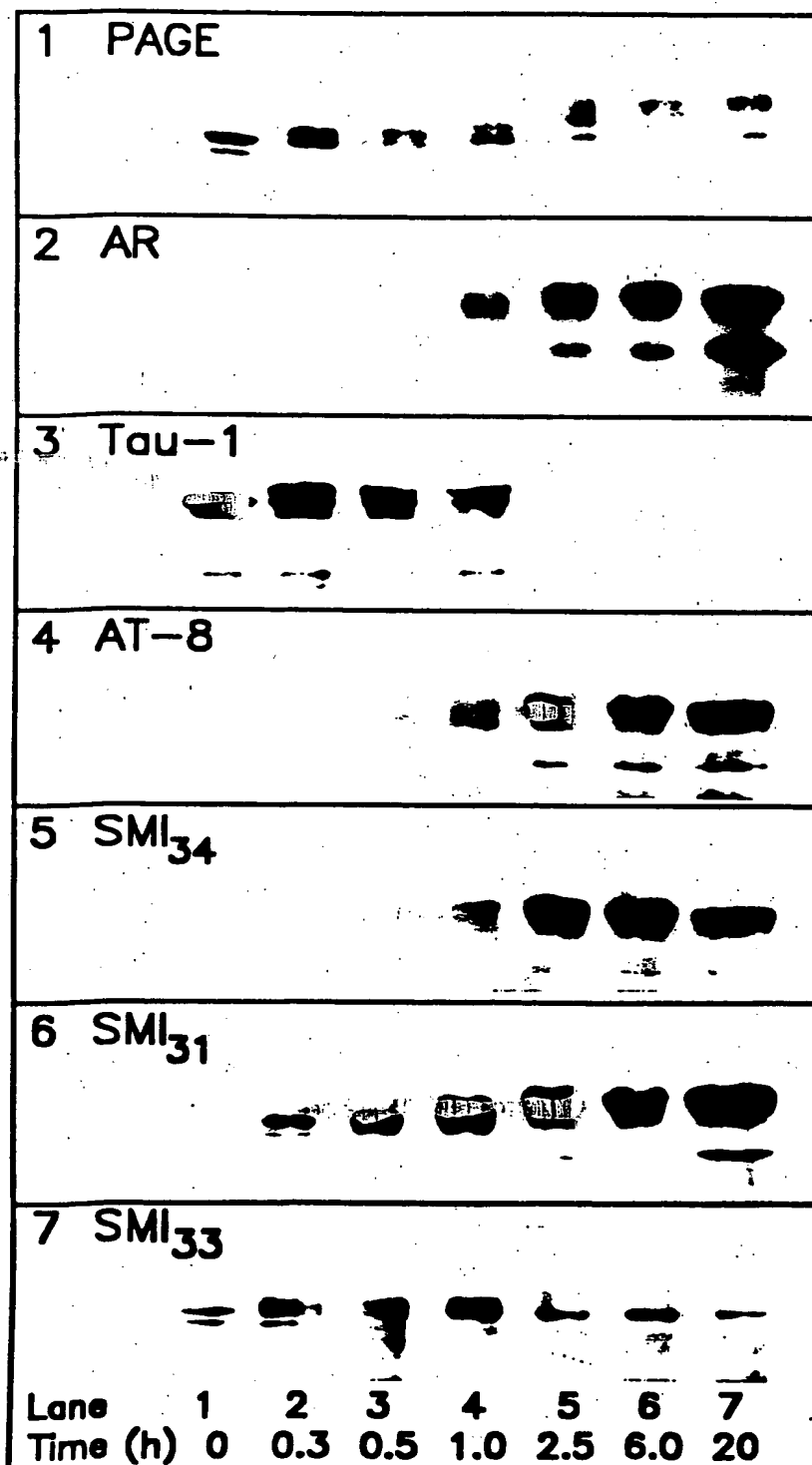


FIGURE 29A  
[Fig. 29a]

FIGURE 29B  
[Fig. 29b]

FIGURE 29C  
[Fig. 29c]

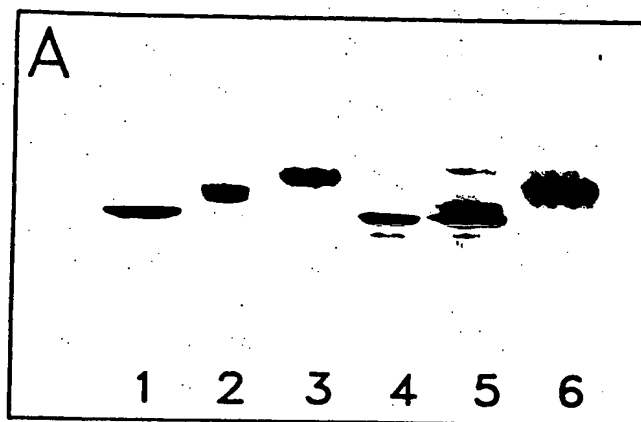
FIGURE 29D  
[Fig. 29d]

FIGURE 29E  
[Fig. 29e]

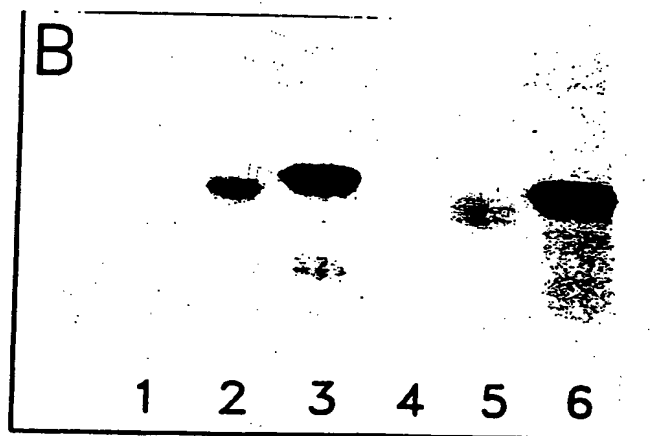
FIGURE 29F  
[Fig. 29f]

FIGURE 29G  
[Fig. 29g]

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[Fig. 30a]  
FIGURE 30A



[Fig. 30b]  
FIGURE 30B

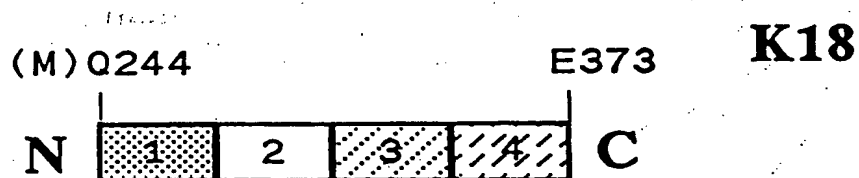
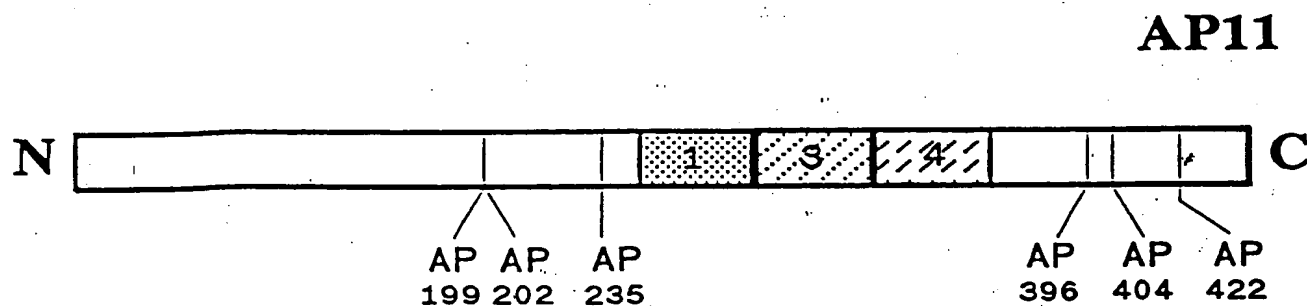
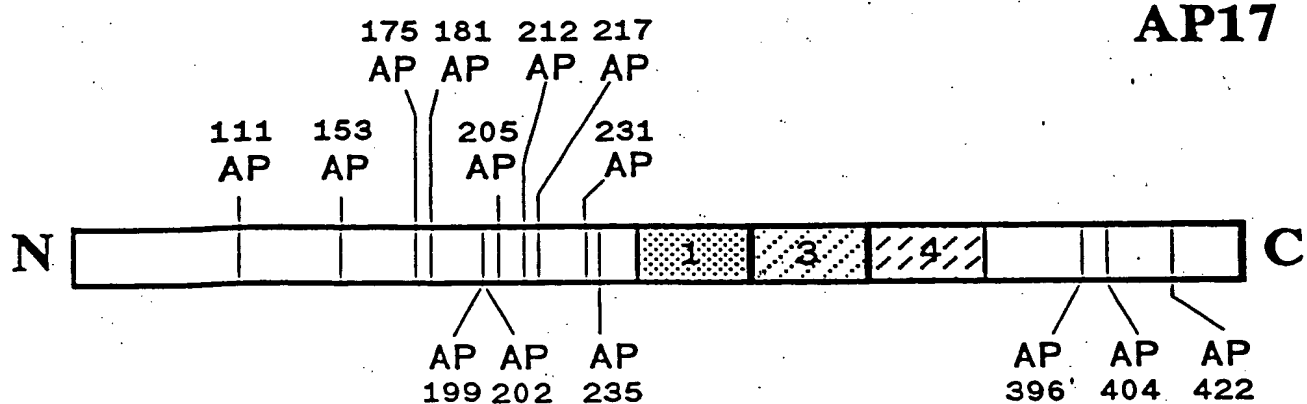
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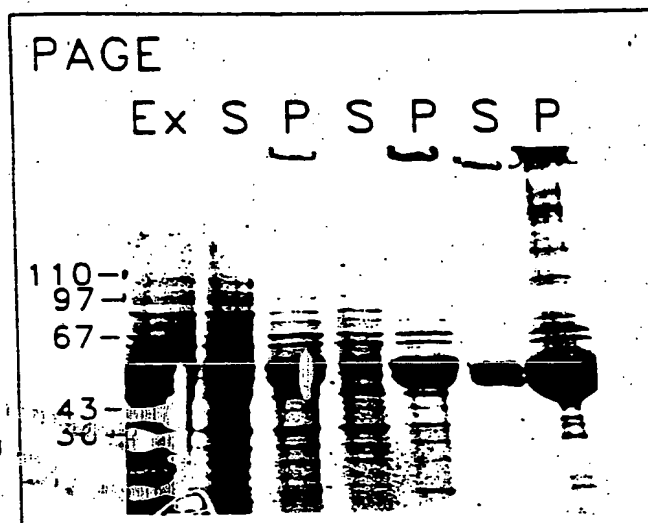
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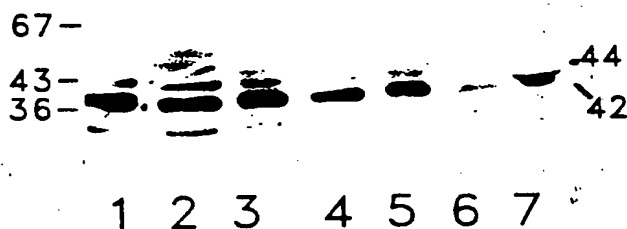
[Fig. 31]  
FIGURE 31

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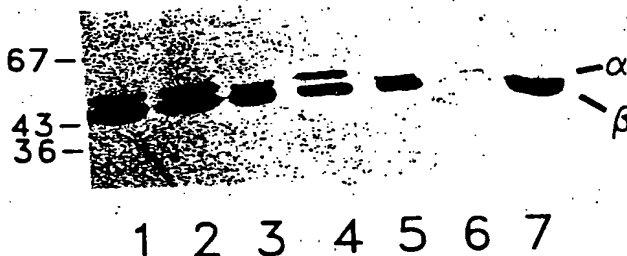
[Fig. 32a]  
FIGURE 32A

Blot MAPK



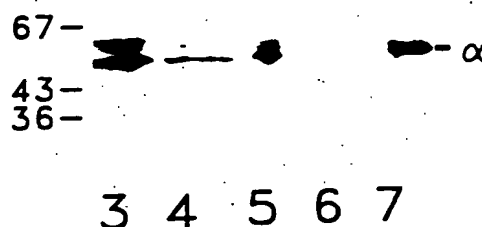
[Fig. 32b]  
FIGURE 32B

Blot GSK  $\beta$



[Fig. 32c]  
FIGURE 32C

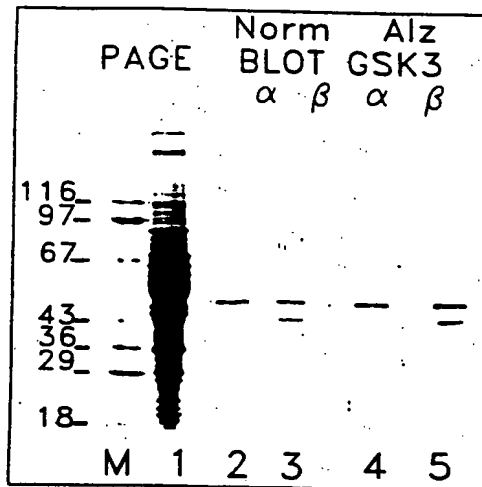
Blot GSK  $\alpha$



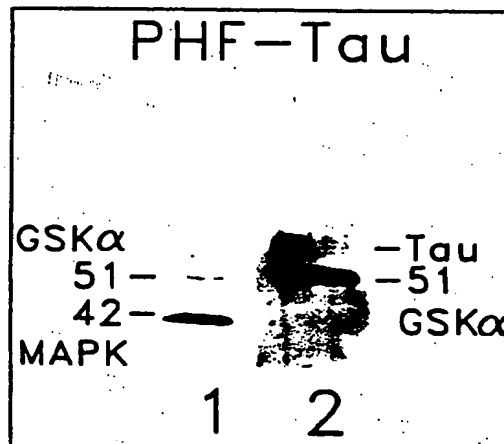
[Fig. 32d]  
FIGURE 32D

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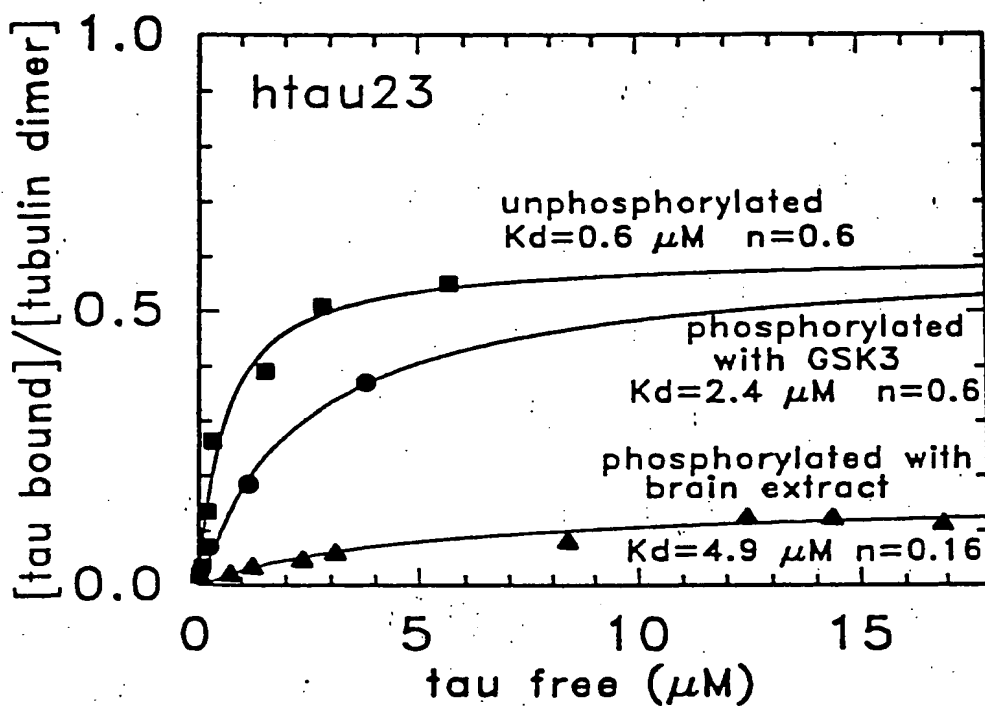


[Fig. 33a]  
FIGURE 33A



[Fig. 33b]  
FIGURE 33B

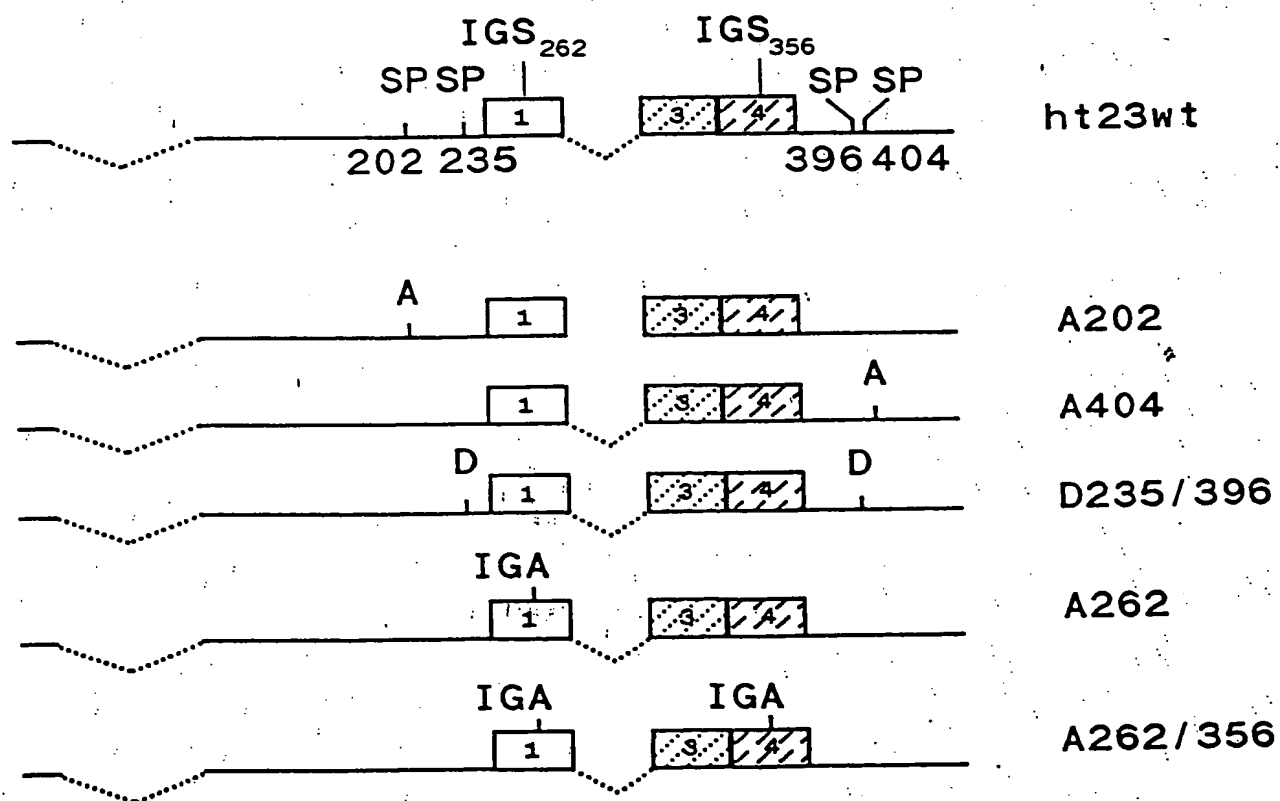
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[Fig. 34]  
FIGURE 34

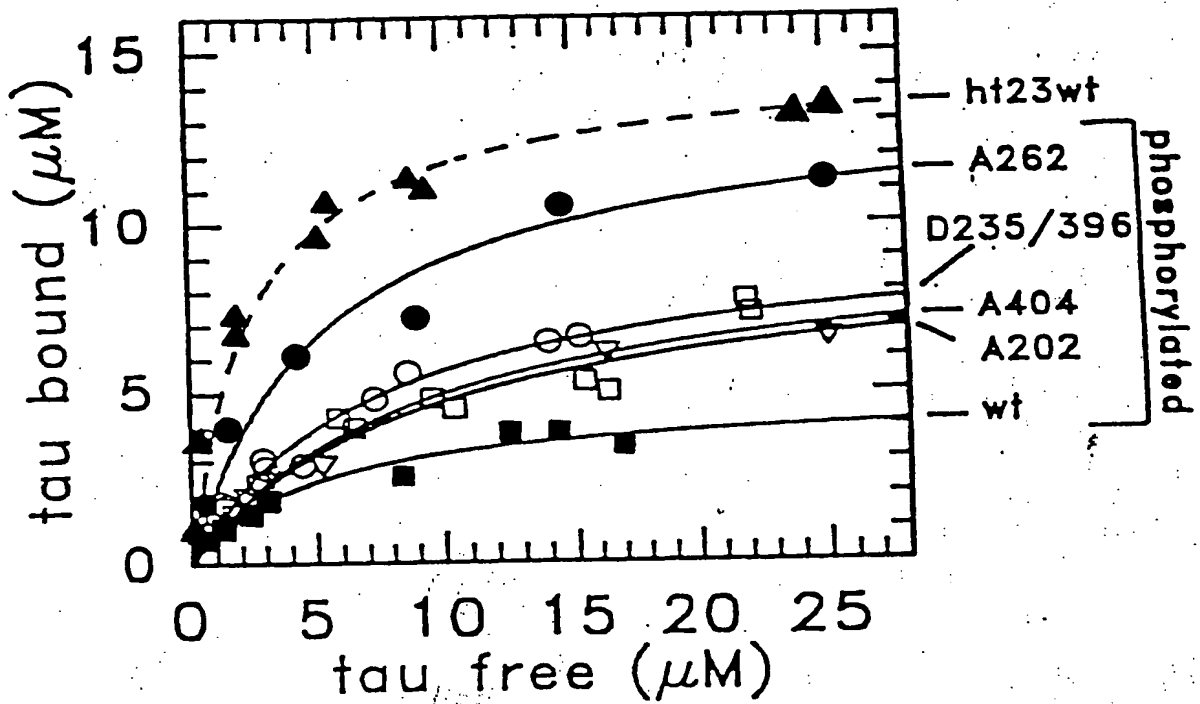
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TREATMENT OF ALZHEIMER'S DISEASE  
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**Fig. 35a**  
FIGURE 35A

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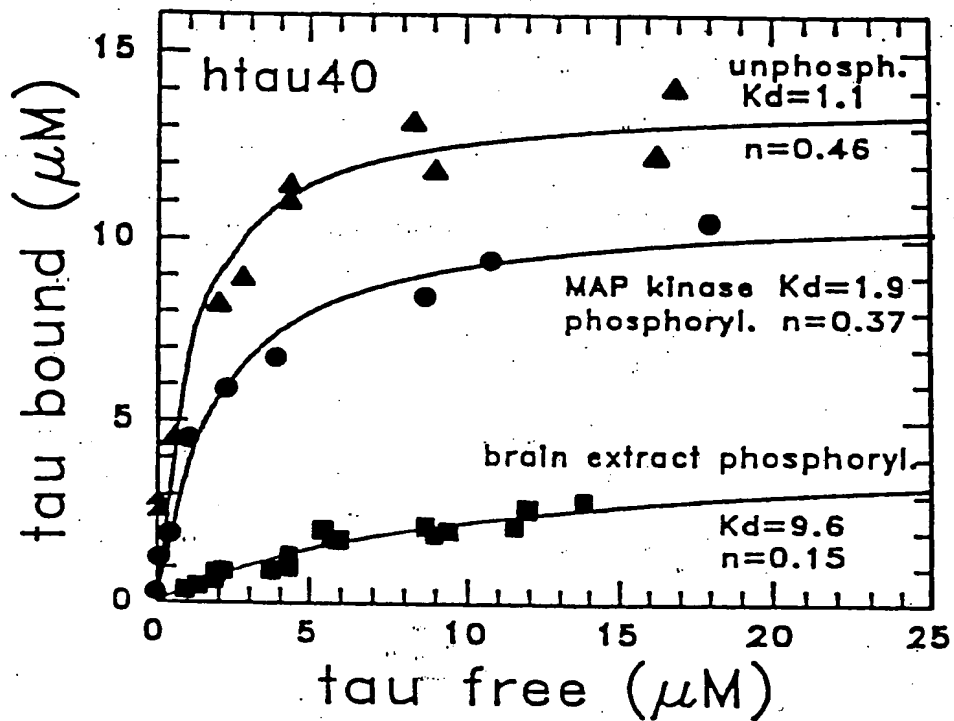


[Fig. 35b]

FIGURE 35B



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[Fig. 36]  
FIGURE 36

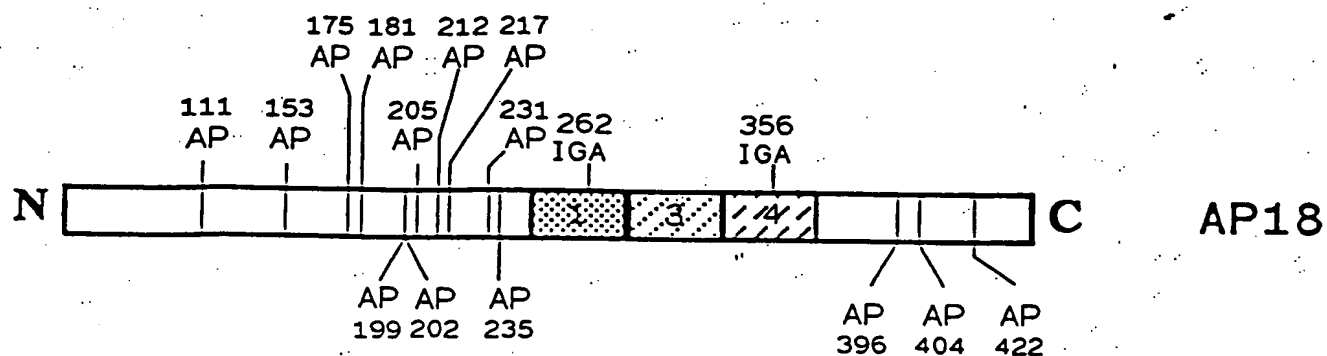
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TREATMENT OF ALZHEIMER'S DISEASE

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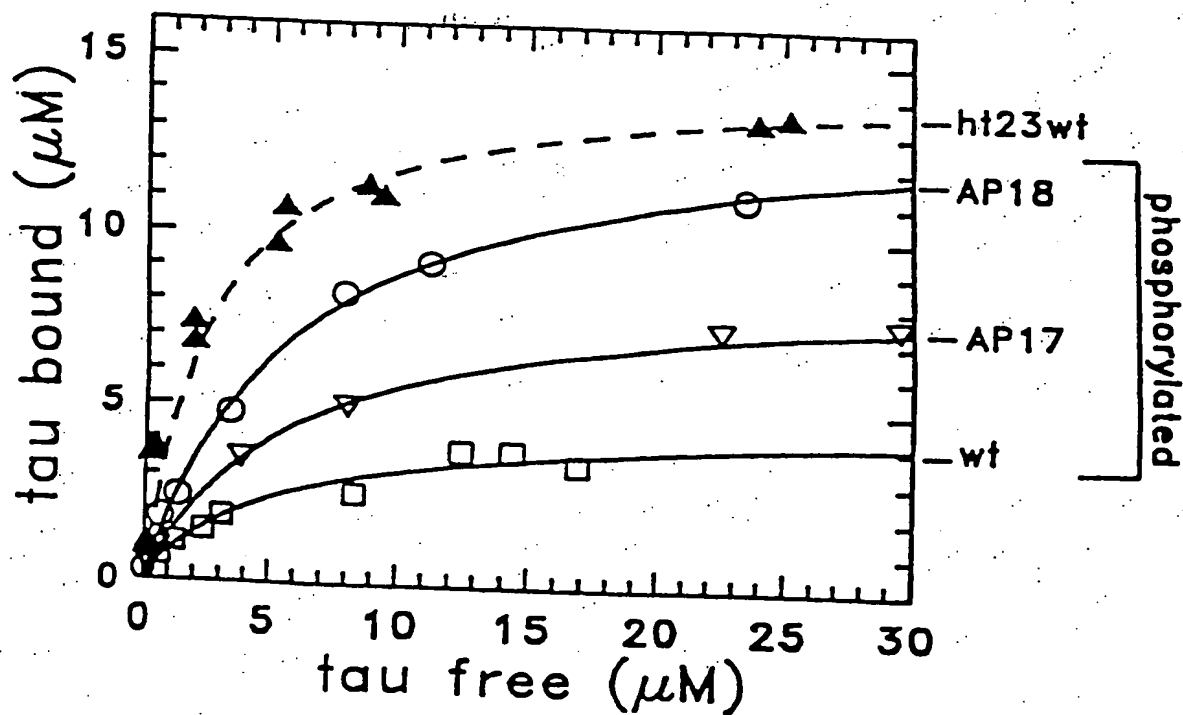
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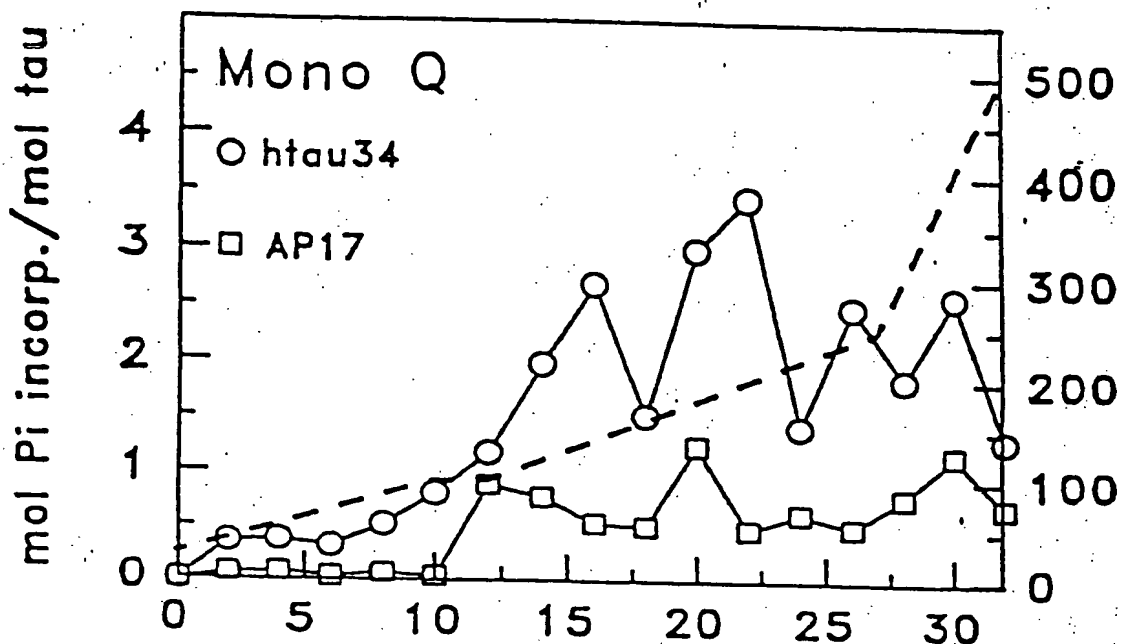
**Fig. 37a**  
FIGURE 37A

FIGURE 37B

**Fig. 37b**



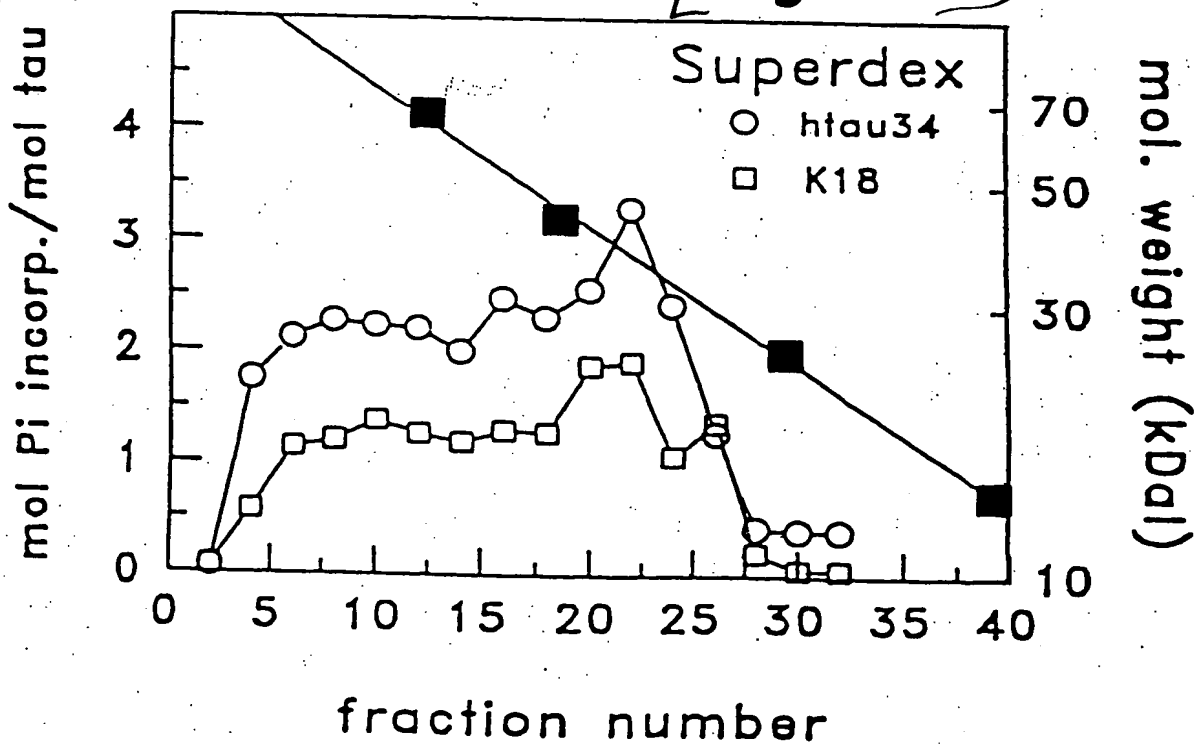
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fraction number

[Fig. 38a] FIGURE 38A

FIGURE 38B [Fig. 38b]



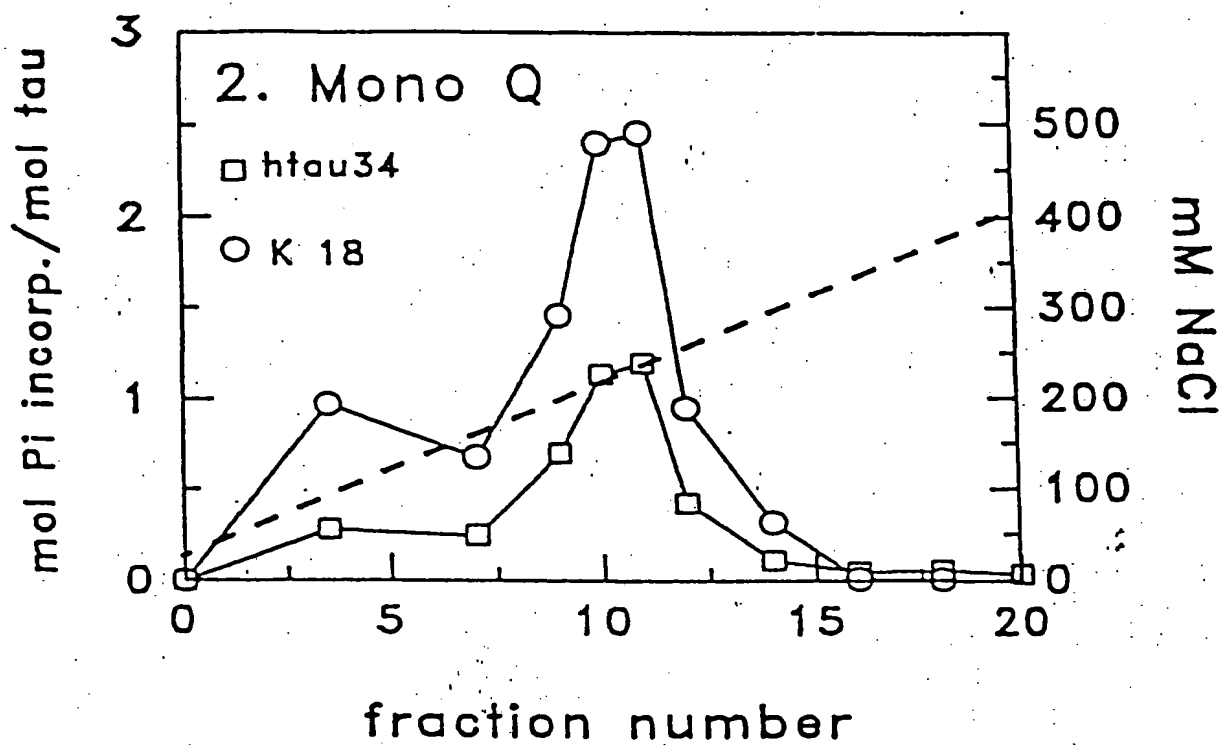
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[Fig. 38c]

FIGURE 38C

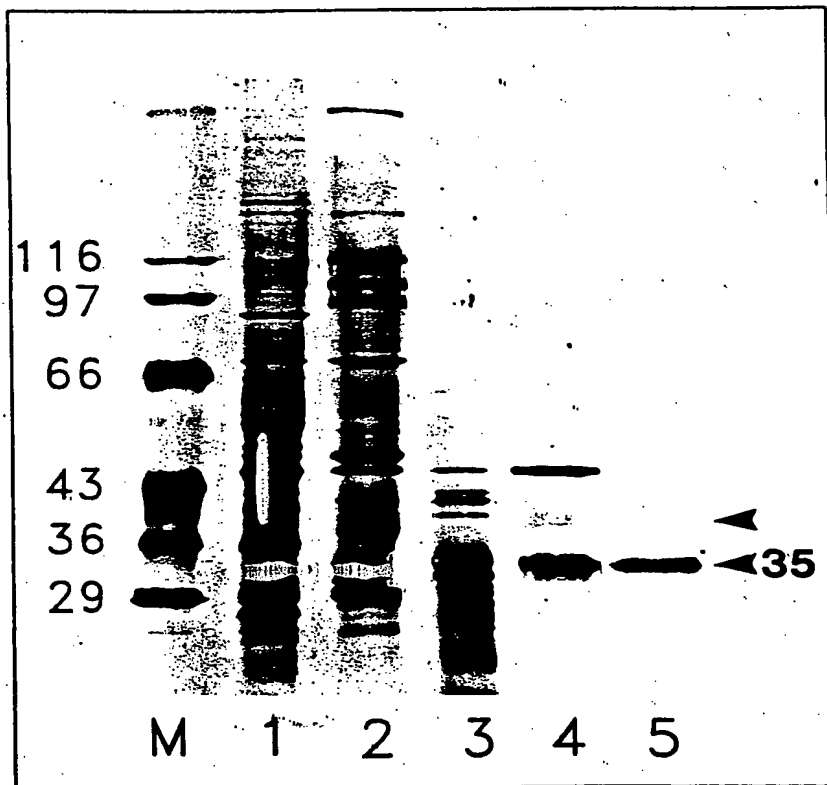
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TREATMENT OF ALZHEIMER'S DISEASE

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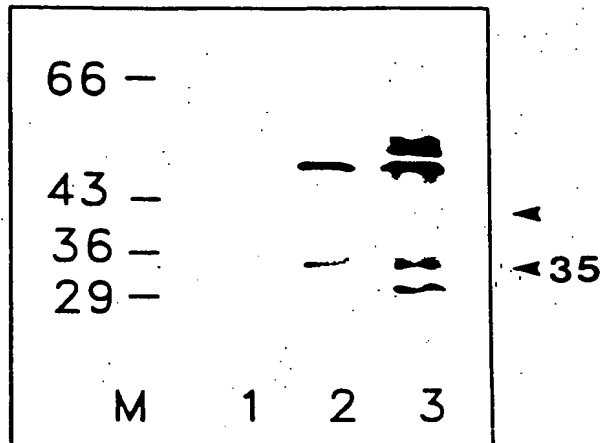


[Fig. 38d]

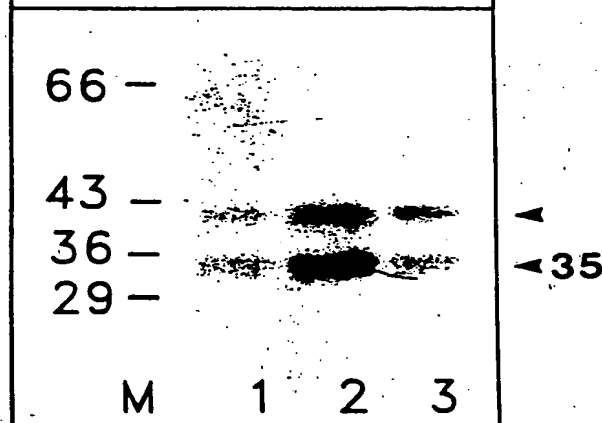
FIGURE 38 D

NOVEL TOOLS FOR THE DIAGNOSIS AND  
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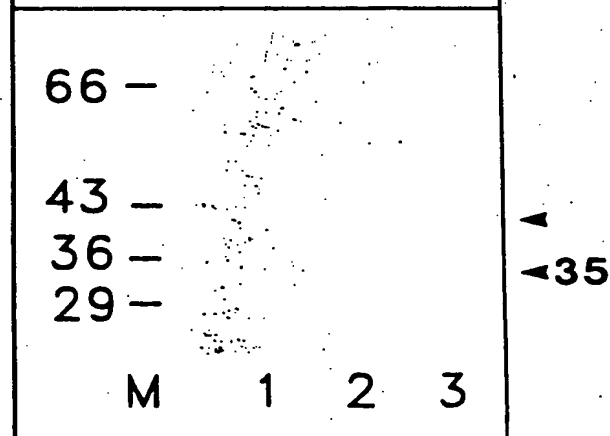
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**[Fig. 39a]**  
FIGURE 39A



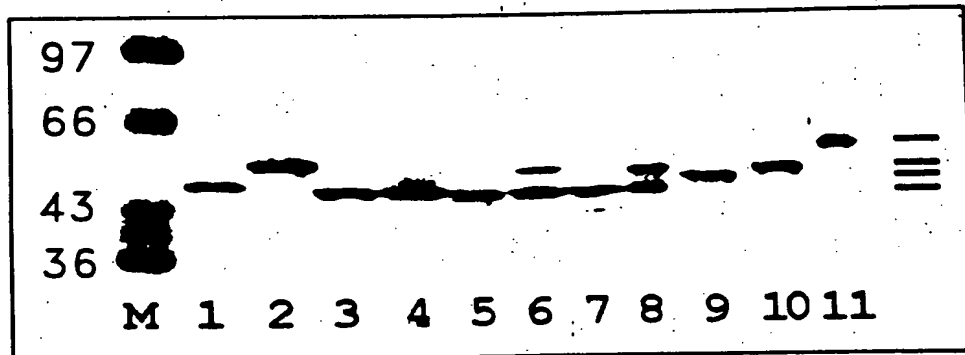
**[Fig. 39b]**  
FIGURE 39B



**[Fig. 39c]**  
FIGURE 39C

NOVEL TOOLS FOR THE DIAGNOSIS AND  
TREATMENT OF ALZHEIMER'S DISEASE  
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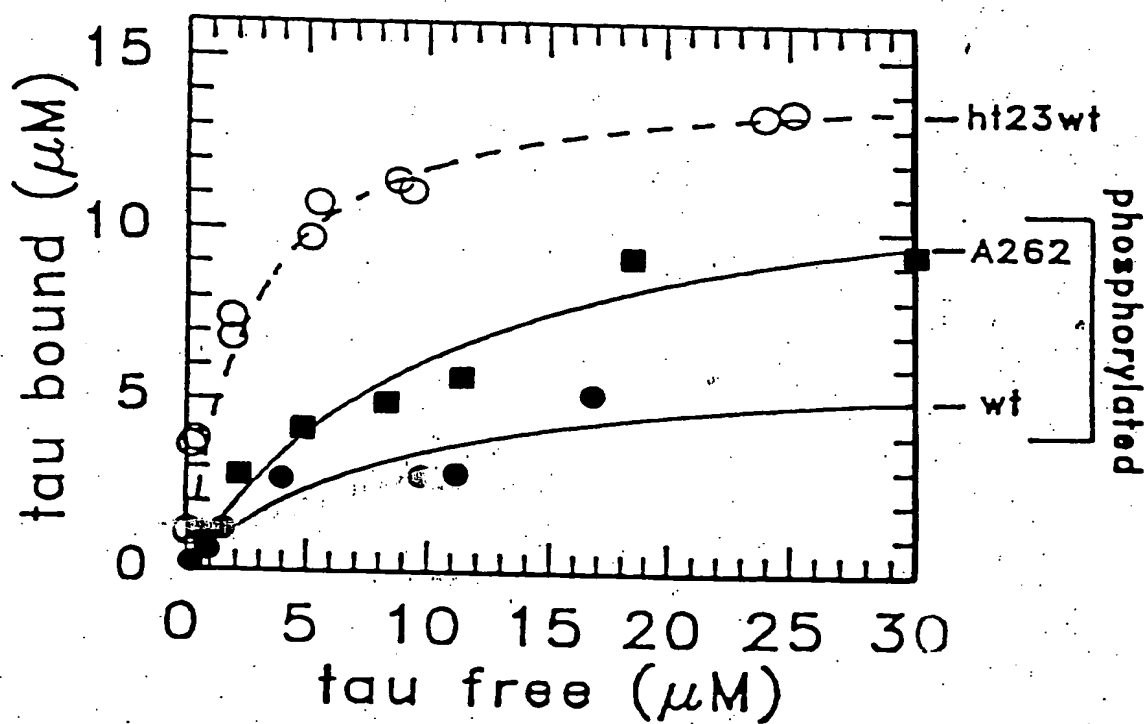
[Fig. 40a]

FIGURE 40A

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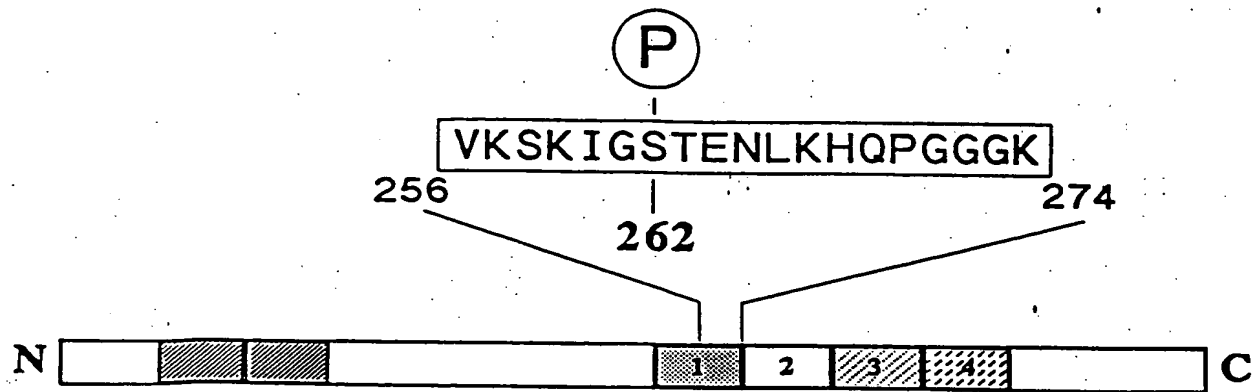
FIGURE 40B

[Fig. 40b]





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[Fig. 41]

FIGURE 41

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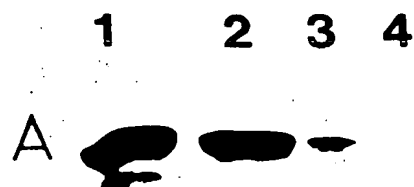


FIGURE 42A

[Fig. 42a]

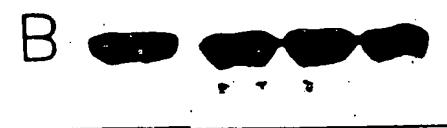


FIGURE 42B

[Fig. 42b]

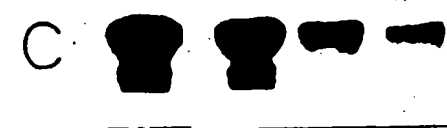


FIGURE 42C

[Fig. 42c]



FIGURE 42D

[Fig. 42d]

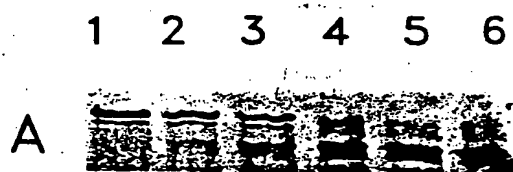


FIGURE 43A

[Fig. 43a]

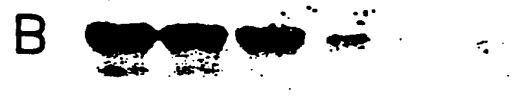


FIGURE 43B

[Fig. 43b]

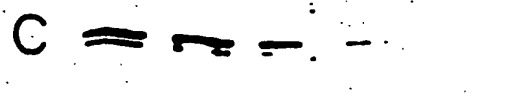


FIGURE 43C

[Fig. 43c]

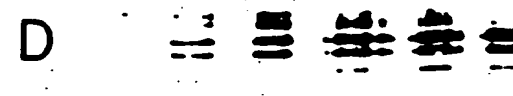


FIGURE 43D

[Fig. 43d]

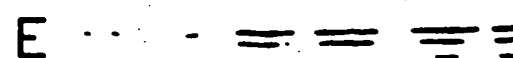


FIGURE 43E

[Fig. 43e]

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FIGURE 44A

[Fig. 44a]

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Dephosph. kinetics of mapk-  
phosph. htau 40 with PP2a

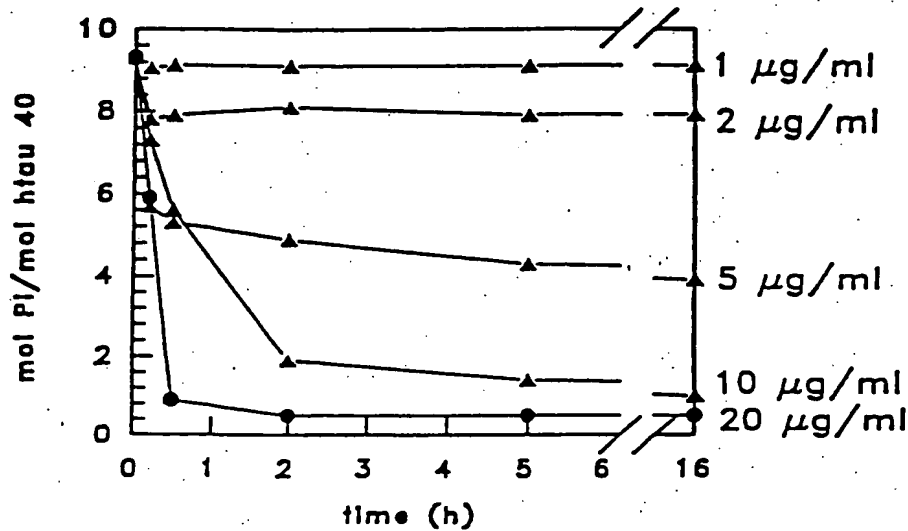
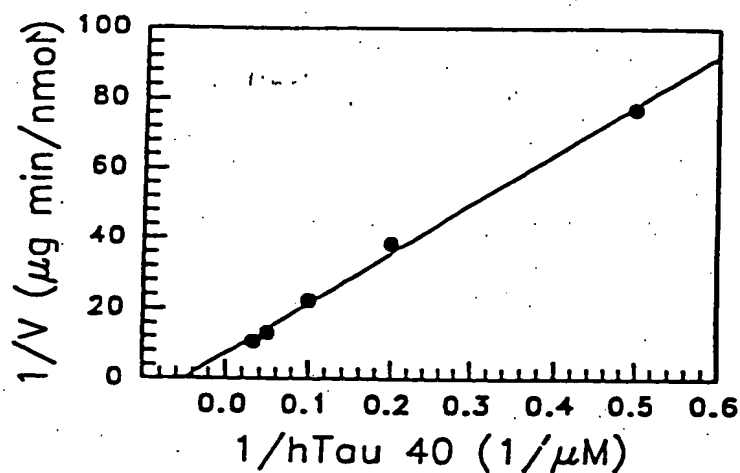


FIGURE 44B

[Fig. 44b]



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FIGURE 45A

Fig. 45a

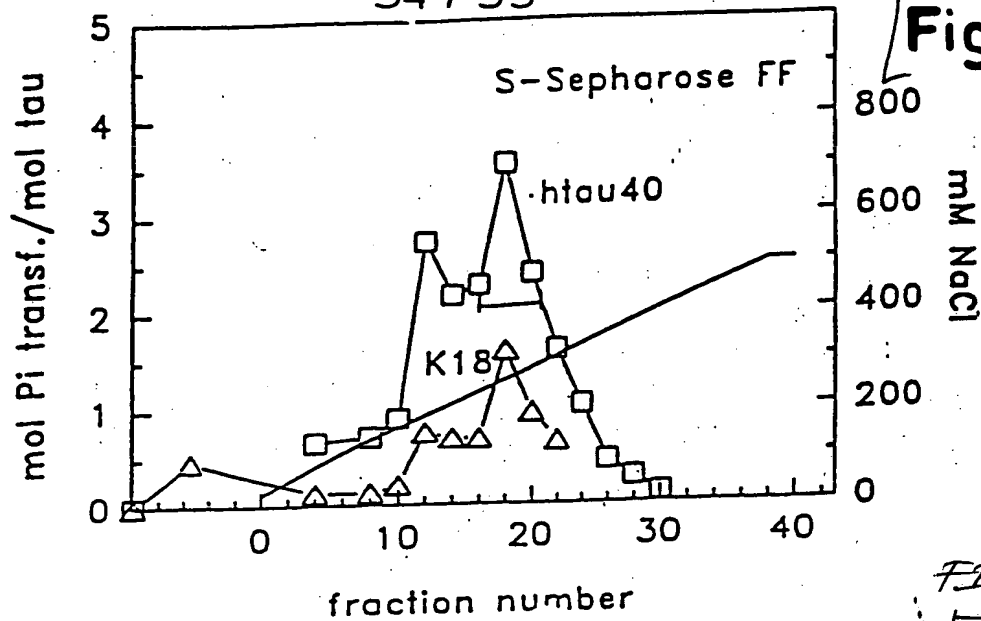


FIGURE 45B

Fig. 45b

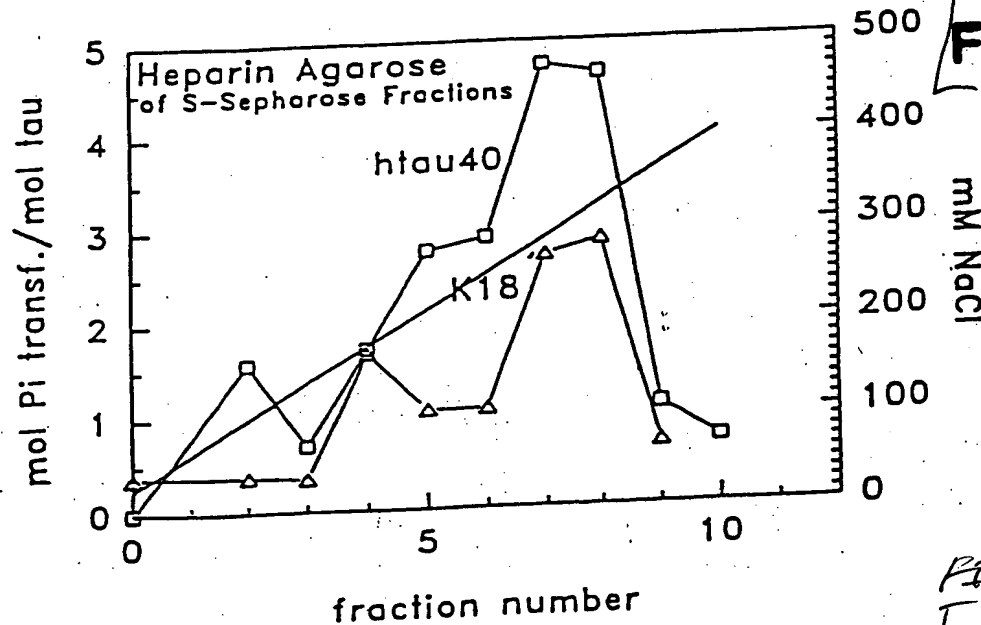
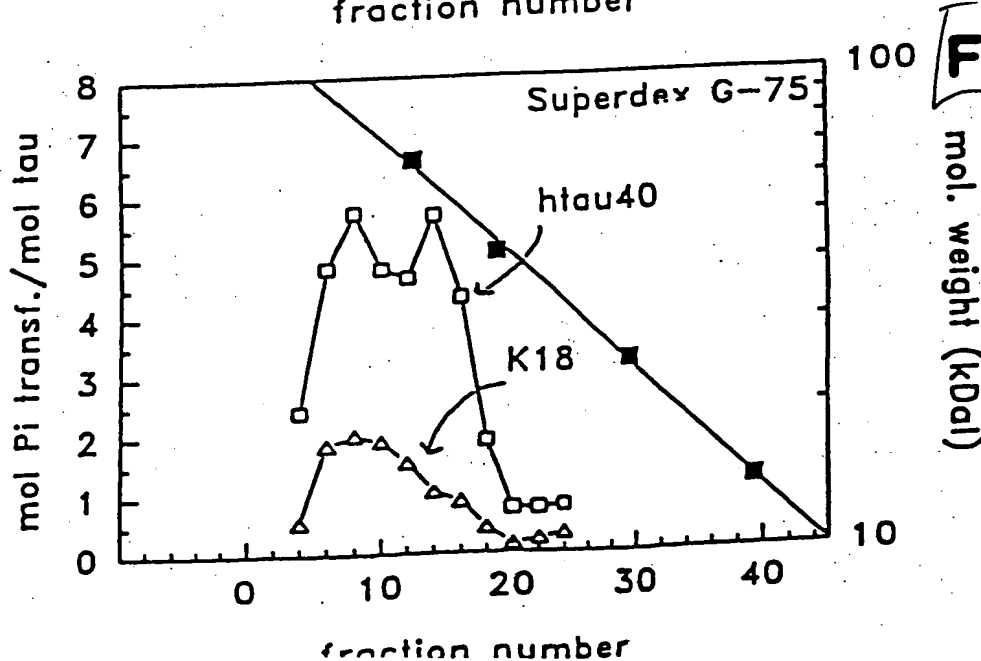


FIGURE 45C

Fig. 45c



NOVEL TOOLS FOR THE DIAGNOSIS AND  
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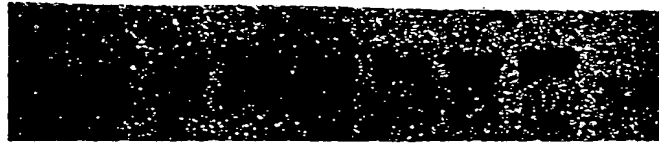


FIGURE 46A

Fig. 46a

2

AR



FIGURE 46B

Fig. 46b

3

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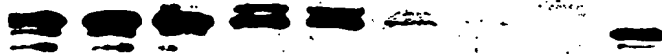


FIGURE 46C

Fig. 46c

4

AT-8



FIGURE 46D

Fig. 46d

LANE	1	2	3	4	5	6	7	8	9
TIME (h)	0	0.2	0.5	1.5	3	6	10	24	0